

**CYCLOALKYL, LACTAM, LACTONE AND RELATED
COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING
SAME, AND METHODS FOR INHIBITING β -AMYLOID PEPTIDE
RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. § 1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025, filed December 23, 1996.

Field of the Invention

This invention relates to compounds which inhibit β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease.

References

The following publications, patents and patent applications are cited in this application as superscript numbers:

- 5
- 10 ¹ Glennner, et al., *Biochem. Biophys. Res. Commun.*, 120:885-890 (1984)
- ² U.S. Patent No. 4,666,829
- 15 ³ Selkoe, *Neuron*, 6:487-498 (1991)
- ⁴ Goate, et al., *Nature*, 349:704-706 (1990)
- ⁵ Chartier Harlan, et al., *Nature*, 353:844-846 (1989)
- 20 ⁶ Murrell, et al., *Science*, 254:97-99 (1991)

- 7 Mullan, et al., *Nature Genet.*, 1:345-347 (1992)
- 8 Schenk, et al., International Patent Application Publication No.
5 WO 94/10569, "*Methods and Compositions for the Detection of Soluble β -Amyloid Peptide*", published 11 May 1994
- 9 Selkoe, Scientific American, "*Amyloid Protein and Alzheimer's Disease*", pp. 2-8. November, 1991
- 10 *Tetrahedron Letters*, 34(48), 7685 (1993)
- 11 Losse, et al., *Tetrahedron*, 27:1423-1434 (1971)
- 12 Citron, et al., *Nature*, 360:672-674 (1992)
- 15 Hansen, et al., *J. Immun. Meth.*, 119:203-210 (1989)
- 14 U.S. Patent No. 3,598,859
- 20 Ogliaruso and Wolfe, *Synthesis of Lactones and Lactams*, Patai, et al. Editor, J. Wiley & Sons, New York, New York, USA, pp. 1085 et seq. (1993).
- 25 Ugi, et al., *Tetrahedron*, 52(35):11657-11664 (1996)
- 17 Blade-Font, *Tetrahedron Lett.*, 21:2443 (1980).
- 18 Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982)
- 30 Semple, et al., *J. Med. Chem.*, 39:4531-4536 (1996).
- 20 Holladay, et al., *J. Org. Chem.*, 56:3900-3905 (1991).
- 35 Donaruma, et al., *Organic Reactions*, 11:1-156 (1960)
- 22 Wolff, *Organic Reactions*, 3:307-336 (1946)
- 23 Krow, et al., *J. Org. Chem.*, 61:5574-5580 (1996)
- 40 *Tetrahedron*, 35:2433 (1979)
- 25 Gracias, et al., *J. Am. Chem. Soc.*, 117:8047-8048 (1995)
- 26 Milligan, et al., *J. Am. Chem. Soc.*, 117:10449-10459 (1995)
- 45 27 Miller, et al., *J. Am. Chem. Soc.*, 118:9606-9614 (1996)

- 28 March, *Advanced Organic Chemistry, Reaction Mechanisms and Structure*, 2nd Edition, McGraw-Hill Book Company, New York, New York, USA (1977)
- 5 29 Colombo, et al., *Tetrahedron Lett.*, 35(23):4031-4034 (1994)
- 30 Rogriguez, et al., *Tetrahedron*, 52:7727-7736 (1996)
- 10 31 Parsons, et al., *Biochem. Biophys. Res. Comm.*, 117:108-113 (1983)
- 32 Watthey, et al., *J. Med. Chem.*, 28:1511-1516 (1985)
- 33 Armstrong, et al., *Tetrahedron Lett.*, 35:3239 (1994)
- 15 34 King, et al., *J. Org. Chem.*, 58:3384 (1993).
- 35 Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995).
- 20 36 Wada, et al., *Bull. Chem. Soc. Japan*, 46:2833-2835 (1973)
- 37 Gaetzi, *Chem. Abs.*, 66:28690m
- 25 38 Wheeler, et al., *Organic Syntheses*, Coll. Vol. VI, p. 840
- 39 *J. Med. Chem.*, 28(12):1886 (1985)
- 40 Brenner, et al., U.S. Patent No. 2,938,029
- 30 41 Evans, et al., *J. Am. Chem. Soc.*, 112:4011-4030 (1990)
- 42 Micouin, et al., *Tetrahedron*, 52:7719-7726 (1996)
- 43 Butcher, et al., *Tetrahedron Lett.*, 37(37):6685-6688 (1996)
- 35 44 M.L. Reupple, et al., *J. Am. Chem. Soc.*, 93:7021 et seq. (1971)
- 45 P.A.S. Smith, *Organic Reactions*, 3:337-449 (1946)
- 40 46 K. Orito, et al., *Tetrahedron*, 36:1017-1021 (1980)
- 47 Krimm, *Chem. Ber.*, 91:1057 (1958)
- 48 Suda, et al., *J. Chem. Soc. Chem Comm.*, 949-950, (1994)
- 45 49 Barton, et al., *J. Chem. Soc.*, 1764-1767 (1975)

- 50 Kitagawa, et al., *J. Am. Chem. Soc.*, 117:5169-5178 (1975)
- 51 Akhatar, et al., *J. Org. Chem.*, 55:5222-5225 (1990)
- 5 52 Nedenskov, et al., *Acta Chem. Scand.*, 12:1405-1410 (1958)
- 53 Sakakida, et al., *Bull. Chem. Soc. Japan*, 44:478-480 (1971)
- 54 Hoffman, et al., *Tet. Lett.*, 30:4207-4210 (1989)
- 10 55 Vedejs, et al., *Tet. Lett.*, 33:3261-3264 (1992)
- 56 van der Steen, et al., *Tetrahedron*, 47, 7503-7524 (1991)
- 15 57 Hart, et al., *Chem Rev.*, 89:1447-1465 (1989)
- 58 Lowe, et al., *Bioorg. Med. Chem. Lett.*, 4:2877-2882 (1994)
- 59 McKennis, Jr., et al., *J. Org. Chem.*, 28:383-387 (1963)
- 20 60 Shiota, et al., *J. Med. Chem.*, 20:1623-1627 (1977)
- 61 Overberger, et al., *J. Am. Chem. Soc.*, 85:3431 (1963)
- 25 62 Herschmann, *Helv. Chim. Acta*, 32:2537 (1949)
- 63 Overberger, et al., *Macromolecules*, 1:1 (1968)
- 64 Busacca, et al., *Tet. Lett.*, 33:165-168 (1992)
- 30 65 Croisier, et al., U.S. Patent No. 4,080,449
- 66 J.A. Robl, et al., *Tetrahedron Lett.*, 36(10):1593-1596 (1995)
- 35 67 Flynn, et al., *J. Med. Chem.*, 36:2420-2423 (1993)
- 68 Orito, et al., *Tetrahedron*, 36:1017-1021 (1980)
- 69 Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989)
- 40 70 Lowe, et al., *J. Med. Chem.*, 37:3789-3811 (1994)
- 71 Robl, et al., *Bioorg. Med. Chem. Lett.*, 4:1789-1794 (1994)
- 45 72 Skiles, et al., *Bioorg. Med. Chem. Lett.*, 3:773-778 (1993)

- 73 Grunewald, et al., *J. Med. Chem.*, 39(18):3539 (1996)
- 74 Thomas, et al., *J. Chem. Soc.*, Perkin II, 747 (1986)
- 5 75 Warshawsky, et al., *Bioorg. Med. Chem. Lett.*, 6:957-962 (1996)
- 76 Ben-Ishai, et al., *Tetrahedron*, 43:439-450 (1987)
- 77 van Niel et al., *Bioorg. Med. Chem. Lett.*, 5:1421-1426 (1995)
- 10 78 Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989)
- 79 Edwards, et al., *Can. J. Chem.*, 49:1648-1658 (1971)
- 15 80 Milligan, et al., *J. Am. Chem. Soc.*, 117:10449-10459 (1995)
- 81 Curran et al., *Tet. Lett.*, 36:191-194 (1995)
- 20 82 Slusarchyk, et al., *Bioorg. Med. Chem. Lett.*, 5:753-758 (1995)
- 83 Wyvratt, et al., Eur. Pat. Appl. 61187 (1982)
- 84 Cornille, et al., *J. Am. Chem. Soc.*, 117:909-917 (1995)
- 25 85 Kolc, *Coll. Czech. Chem. Comm.*, 34:630 (1969)
- 86 Dickerman, et al., *J. Org. Chem.*, 14:530 (1949)
- 87 Dickerman, et al., *J. Org. Chem.*, 20:206 (1955)
- 30 88 Dickerman, et al., *J. Org. Chem.*, 19:1855 (1954)
- 89 Hoffman, et al., *J. Org. Chem.*, 27:3565 (1962)
- 35 90 Wasserman, et al., *J. Am. Chem. Soc.*, 103:461-2 (1981)
- 91 Crombie, et al., *Tetrahedron Lett.*, 27(42):5151-5154 (1986)
- 92 Yokoo, et al., *Bull. Chem. Soc. Jap.*, 29:631 (1956)
- 40 93 Burkholder, et al., *Biog. Med. Chem. Lett.*, 2:231 (1993)
- 94 Karanewsky, U.S. Patent No. 4,460,579
- 45 95 Kametani, et al., *Heterocycles*, 9:831-840 (1978)

⁹⁶ Yanganasawa, et al., *J. Med. Chem.*, 30:1984-1991 (1987)

⁹⁷ J. Das et al., *Biorg. Med. Chem. Lett.*, 4:2193-2198 (1994)

5 All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

10 State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

25 The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type

(HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the β -amyloid peptide (β AP) or sometimes $A\beta$, $A\beta$ P or $\beta/A4$. β -Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.¹ The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829².

Molecular biological and protein chemical analyses have shown that the β -amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that β -amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β -amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

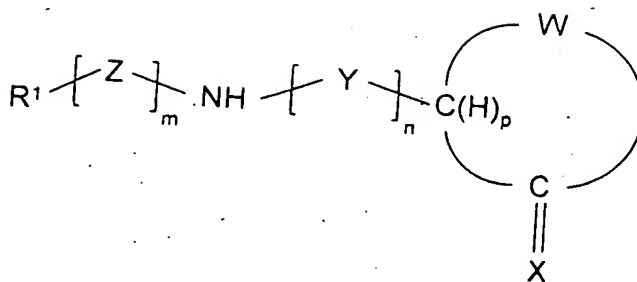
Several lines of evidence indicate that progressive cerebral deposition of β -amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe³. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with

a genetically determined (familial) form of AD (Goate, et al.⁴; Chartier Harlan, et al.⁵; and Murrell, et al.⁶) and is referred to as the Swedish variant. A double mutation changing lysine⁵⁹⁵-methionine⁵⁹⁶ to asparagine⁵⁹⁵-leucine⁵⁹⁶ (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.⁷). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β -amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD in some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β -amyloid peptide fragment can cause AD.

Despite the progress which has been made in understanding the underlying mechanisms of AD and other β -amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β -amyloid peptide release and/or its synthesis *in vivo*.

SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of compounds which inhibit β -amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of AD in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The class of compounds having the described properties are defined by formula I below:



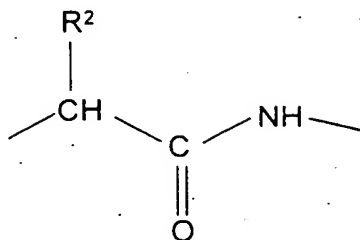
I

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

X is selected from the group consisting of oxo ($=O$), thiooxo ($=S$), hydroxyl ($-H$, $-OH$), thiol (H , $-SH$) and hydro (H , H);

Y is represented by the formula:



15 wherein each R^2 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

Z is represented by the formula $-\text{T}-\text{CX}'\text{X}''\text{C}(\text{O})-$ where T is selected from the group consisting of a bond covalently linking R^1 to $-\text{CX}'\text{X}''-$, oxygen, sulfur, $-\text{NR}^5$ where R^5 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

20

X' is hydrogen, hydroxy or fluoro,

X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

m is an integer equal to 0 or 1;

25 n is an integer equal to 0, 1 or 2;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and $-\text{C}(\text{H})_p\text{C}(=\text{X})-$ is unsaturated at the carbon atom of ring attachment to Y and when p is one, the ring is saturated at the carbon atom of ring attachment to Y,

30 with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W, together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a 2-(S)-indanol group;

B. when R^1 is phenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a trans-2-hydroxy-cyclohex-1-yl group;

5 C. when R^1 is phenyl, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 0, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a gamma-butyrolactone group or a 5,5-dimethyl-gamma-butyrolactone group;

D. when R^1 is phenyl, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 0, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a ϵ -caprolactam group;

10 E. when R^1 is cyclopropyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an N -methylcaprolactam group;

F. when R^1 is 4-chlorobenzoyl- CH_2- , R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

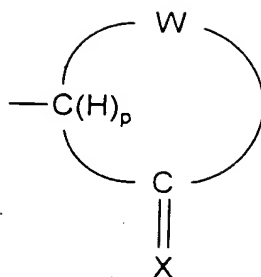
15 G. when R^1 is 2-phenylphenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

20 H. when R^1 is $\text{CH}_3\text{OC}(\text{O})\text{CH}_2-$, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 2,3-dihydro-1-(*t*-butyl $\text{C}(\text{O})\text{CH}_2-$)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

25 I. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $\text{CH}_3\text{OC}(\text{O})\text{CH}_2-$, 4- HOCH_2 -phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or $\text{CH}_3\text{S}-$, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a 2,3-dihydro-1-(N,N -diethylamino- CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

J. when R^1 is 2,6-difluorophenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}(\text{OH})\text{C}(\text{O})-$, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a 2,3-dihydro-1-(N,N -diethylamino- CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one,

30 K. when m is 1 and n is 1, then



does not equal cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

Accordingly, in one of its method aspects, this invention is directed to a method for inhibiting β -amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds of formula I above effective in inhibiting the cellular release and/or synthesis of β -amyloid peptide.

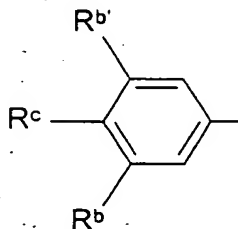
Because the *in vivo* generation of β -amyloid peptide is associated with the pathogenesis of AD^{8,9}, the compounds of formula I can also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. Accordingly, in another of its method aspects, this invention is directed to a prophylactic method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

In yet another of its method aspects, this invention is directed to a therapeutic method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

In formula I above, when m is zero (i.e., there is a covalent bond from R^1 to NH), R^1 is preferably aryl (including substituted aryl) or heteroaryl (including substituted heteroaryl). In this embodiment, further preferred R^1 groups include

(a) phenyl,

(b) a substituted phenyl group of the formula:



wherein R^c is selected from the group consisting of acyl, alkyl, alkoxy, alkylalkoxy, azido, cyano, halo, hydrogen, nitro, trihalomethyl, thioalkoxy, and wherein R^b and R^c are fused to form a heteroaryl or heterocyclic ring with the phenyl ring wherein the heteroaryl or heterocyclic ring contains from 3 to 8 atoms of which from 1 to 3 are heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur

R^b and R^b are independently selected from the group consisting of hydrogen, halo, nitro, cyano, trihalomethyl, alkoxy, and thioalkoxy with the proviso that when R^c is hydrogen, then R^b and R^b are either both hydrogen or both substituents other than hydrogen,

(c) 2-naphthyl,

(d) 2-naphthyl substituted at the 4, 5, 6, 7 and/or 8 positions with 1 to 5 substituents selected from the group consisting alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, thioalkoxy, aryl, and heteroaryl,

(e) heteroaryl, and

5 (f) substituted heteroaryl containing 1 to 3 substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, cyano, halo, nitro, heteroaryl, thioalkoxy, thioaryloxy provided that said substituents are not *ortho* to the heteroaryl attachment to the -NH group.

10 When m is zero, particularly preferred substituted phenyl R^1 groups include mono-, di- and tri-substituted phenyl groups including 3,5-disubstituted phenyls such as 3,5-dichlorophenyl, 3,5-difluorophenyl, 3,5-di(trifluoromethyl)-phenyl, etc.; 3,4-disubstituted phenyls such as 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-(trifluoromethyl)-4-chlorophenyl, 3-chloro-4-cyanophenyl,
15 3-chloro-4-iodophenyl, 3,4-methylenedioxyphenyl, etc.; 4-substituted phenyls such as 4-azidophenyl, 4-bromophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-ethylphenyl, 4-fluorophenyl, 4-iodophenyl, 4-(phenylcarbonyl)phenyl, 4-(1-ethoxy)ethylphenyl, etc., 3,4,5-trisubstituted phenyls such as 3,4,5-trifluorophenyl, 3,4,5-trichlorophenyl, etc.

20

Specific R^1 groups for when m is zero include 3,4-dichlorophenyl, 4-phenylfurazan-3-yl, and the like.

When m is zero, other preferred R^1 substituents include, by way of
25 example, 2-naphthyl, quinolin-3-yl, 2-methylquinolin-6-yl, benzothiazol-6-yl, 5-indolyl, phenyl, and the like.

When m is one, preferred R^1 groups include unsubstituted aryl groups such as phenyl, 1-naphthyl, 2-naphthyl, etc.; substituted aryl groups such as
30 monosubstituted phenyls (preferably substituents at 3 or 5 positions); disubstituted phenyls (preferably substituents at 3 and 5 positions); and

trisubstituted phenyls (preferably substituents at the 3,4,5 positions).

Preferably, the substituted phenyl groups do not include more than 3 substituents. Examples of substituted phenyls include, for instance,

2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl; 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl; 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl, 2-fluoro-3-trifluoromethylphenyl,

When *m* is one, other preferred R¹ groups include, by way of example, adamantyl, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, 4-phenyl-*n*-butyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-valeryl, *n*-hexyl, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl.

-CH₂CH₂-cyclohexyl, -CH₂CH₂-cyclopentyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thien-2-yl, thien-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, thionaphthen-3-yl, 5 thionaphthen-4-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thien-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-4-yl, indol-3-yl, 1-phenyl-tetraol-5-yl, allyl, 2-(cyclohexyl)ethyl, (CH₃)₂CH=CHCH₂CH₂CH(CH₃)-, ϕ C(O)CH₂-, thien-2-yl-methyl, 2-(thien-2-yl)ethyl, 3-(thien-2-yl)-*n*-propyl, 2-(4-nitrophenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 10 norboran-2-yl, (4-methoxyphenyl)methyl, (2-methoxyphenyl)methyl, (3-methoxyphenyl)methyl, (3-hydroxyphenyl)methyl, (4-hydroxyphenyl)methyl, (4-methoxyphenyl)methyl, (4-methylphenyl)methyl, (4-fluorophenyl)methyl, (4-fluorophenoxy)methyl, (2,4-dichlorophenoxy)ethyl, (4-chlorophenyl)methyl, (2-chlorophenyl)methyl, (1-phenyl)ethyl, (1-(*p*-chlorophenyl)ethyl, (1-trifluoromethyl)ethyl, (4-methoxyphenyl)ethyl, CH₃OC(O)CH₂-, benzylthiomethyl, 5-(methoxycarbonyl)-*n*-pentyl, 3-(methoxycarbonyl)-*n*-propyl, indan-2-yl, (2-methylbenzofuran-3-yl), methoxymethyl, CH₃CH=CH-, CH₃CH₂CH=CH-, (4-chlorophenyl)C(O)CH₂-, (4-fluorophenyl)C(O)CH₂-, (4-methoxyphenyl)C(O)CH₂-, 4-(fluorophenyl)-20 NHC(O)CH₂-, 1-phenyl-*n*-butyl, (ϕ)₂CHNHC(O)CH₂CH₂-, (CH₃)₂NC(O)CH₂-, (ϕ)₂CHNHC(O)CH₂CH₂-, methylcarbonylmethyl, (2,4-dimethylphenyl)C(O)CH₂-, 4-methoxyphenyl-C(O)CH₂-, phenyl-C(O)CH₂-, CH₃C(O)N(ϕ)-, ethenyl, methylthiomethyl, (CH₃)₃CNHC(O)CH₂-, 4-fluorophenyl-C(O)CH₂-, diphenylmethyl, phenoxymethyl, 3,4-25 methylenedioxyphenyl-CH₂-, benzo[b]thiophen-3-yl, (CH₃)₃COC(O)NHCH₂-, *trans*-styryl, H₂NC(O)CH₂CH₂-, 2-trifluoromethylphenyl-C(O)CH₂-, ϕ C(O)NHCH(ϕ)CH₂-, mesityl, CH₃CH(=NHOH)CH₂-, 4-CH₃- ϕ -NHC(O)CH₂CH₂-, ϕ C(O)CH(ϕ)CH₂-, (CH₃)₂CHC(O)NHCH(ϕ)-, CH₃CH₂OCH₂-, CH₃OC(O)CH(CH₃)(CH₃)₃-, 2,2,2-trifluoroethyl, 1-30 (trifluoromethyl)ethyl, 2-CH₃-benzofuran-3-yl, 2-(2,4-dichlorophenoxy)ethyl, ϕ SO₂CH₂-, 3-cyclohexyl-*n*-propyl, CF₃CH₂CH₂CH₂- and N-pyrrolidinyl.

Still other preferred R¹ groups include those set forth in the Tables below.

When *n* is one or two, each R² is preferably (and independently for *n* = 2) selected from the group consisting of alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic.

Particularly preferred R² substituents include, by way of example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (*cis* and *trans*), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino), *p*-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl, thien-3-yl, and the like.

Compounds of this invention include, by way of example,

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminodibenzosuberane

5 1-(R)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-(S)-indanol

1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-(R)-indanol

10 1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-2-indanol

2-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-1-cyclohexanol

15 1-(R,S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-1,2,3,4-tetrahydro-2-naphthol

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminobenz[f]cycloheptan-2-ol

20 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol

1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-aminoindan-2-one

25 2-(N'-(phenylacetyl)-L-alaninyl)aminocyclohexan-1-one

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one

30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino- γ -butyrolactone

3-(N'-(3,4-dichlorophenyl)-L-alaninyl)amino- γ -butyrolactone

35 4-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1,1-dimethyl-3-isochromanone

4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,1-dimethyl-3-isochromanone

40 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino- γ -butyrolactam

3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino- δ -valerolactam

45 1-benzyl-3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino- δ -valerolactam

3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-4-methyl- ϵ -caprolactam

- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroquinolin-2-one
- 5 1-benzyl-3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroquinolin-2-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroisoquinolin-3-one
- 10 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 15 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-6-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one
- 20 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-phenethyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 25 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 30 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-6-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 35 (N'-(3,5-difluorophenylacetyl)-L-alaninyl)-(9-aminofluoren-1-yl)glycine δ -lactam
- 40 3-(N'-(phenylacetyl)-L-alaninyl)amino- ϵ -caprolactam
- 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino- ϵ -caprolactam
- 45 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl- ϵ -caprolactam

- 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(2-methoxyethyl)-
ε-caprolactam
- 5 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-ε-
caprolactam
- 3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-ethyl-ε-caprolactam
- 10 3-N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-ethyl-ε-caprolactam
- 3-N'-(3,5-difluorophenylacetyl)-L-alaninyl-amino)-7-benzyl-ε-
caprolactam
- 15 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-4,7-
methano-ε-caprolactam
- 3-(S)-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1-benzyl-ε-caprolactam
- 20 3-(S)-(N'-(cyclopentylacetyl)-L-phenylglycinyl)amino-1-benzyl-ε-
caprolactam
- 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(2-phenethyl)-ε-
caprolactam
- 25 3-(S)-(N'-(cyclopentylacetyl)-L-phenylglycinyl)amino-1-(2-phenethyl)-ε-
caprolactam
- 3-(N'-(3,4-dichlorophenyl)-D,L-alaninyl)amino-ε-caprolactam
- 30 3-(S)-(N'-(cyclopropylacetyl)-L-phenylglycinyl)amino-1-methyl-ε-
caprolactam
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-8-octanelactam
- 35 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-benzyl-1,2,3,4-
tetrahydroisoquinolin-3-one
- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-1,2,3,4-
tetrahydroisoquinolin-3-one
- 40 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2-methyl-1-phenyl-
1,2,3,4-tetrahydroisoquinolin-3-one
- 45 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-2-yl)-1,2,3,4-
tetrahydroisoquinolin-3-one

- 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinolin-3-one
- 5 4-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinolin-3-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-1-methyl-2-indolinone
- 10 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl
- 15 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-4-phenyl-3,4-*trans*-dihydrocarbostyryl
- 20 1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one
- 1-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-3-ethyl-4'-fluoro-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one
- 25 3-(3,5-difluorophenylacetyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one
- 3-(N'-(cyclopentylacetyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 35 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 40 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 3-(3,5-difluorophenylacetyl)amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 45 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

- 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5-oxa-
1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 5 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-5-thia-
1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}-amino-3,3-dimethyl-5,7-
dihydro-6H-benz[b]azepin-6-one
- 10 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-3,3,7-trimethyl-5,7-
dihydro-6H-benz[b]azepin-6-one
- 5-{N'-[(S)-3,5-difluoromandelyl]-L-alaninyl}amino-3,3,7-trimethyl-5,7-
dihydro-6H-benz[b]azepin-6-one
- 15 1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-1,3,4,5-
tetrahydro-2H-3-benzazepin-2-one
- 20 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5,5-dimethyl-
1,3,4,5-tetrahydro-2H-1-benzazepin-2-one
- 5-(S)-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-methyl-5,7-
dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-(S)-[N'-((S) and (R)-3,5-difluorophenyl- α -hydroxyacetyl)-L-
alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(S)-[N'-(3,5-difluorophenyl- α -ketoacetyl)-L-alaninyl]amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(S)-[N'-(3,5-difluorophenylacetyl)-L-valinyl]amino-7-methyl-5,7-
dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(S)-[N'-(3,5-difluorophenylacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-
dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(S)-[N'-((S)-3,5-difluorophenyl- α -hydroxyacetyl)-L-valinyl]amino-7-
methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(S)-[N'-((S)-3,5-difluorophenyl- α -hydroxyacetyl)-L-*tert*-
leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(methoxyacetyl)-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(methylcarboxylate)-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(3,3-dimethyl-2-butanoyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(morpholinylacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(S)-(N'-((S)-(+)-2-Hydroxy-3-methylbutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-[N'-cyclopentyl- α -hydroxyacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-(S)-(N'-((S) and (R)-3,3-dimethyl-2-hydroxybutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-[N'-cyclopentyl- α -hydroxyacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-[N'-cyclopentyl- α -hydroxyacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one
- 25 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-[N'-(2-hydroxy-3-methylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(S)-[N'-((S and R)-2-hydroxy-3,3-dimethylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(4-phenyl-furazan-3-yl)alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one
- 40 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(3,5-difluorophenylacetyl)-L-alaninyl}amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-H-dibenz[b,d]azepin-6-one

- 5- $\{N'-(3,5\text{-difluorophenylacetyl})\text{-L-alaninyl}\}$ amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-alaninyl}\}$ amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-alaninyl}\}$ -amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-alaninyl}\}$ amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-alaninyl}\}$ amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-valinyl}\}$ amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-valinyl}\}$ amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-valinyl}\}$ amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-valinyl}\}$ amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5- $\{N'-[(S)\text{-}3,5\text{-difluoromandelyl}]\text{-L-valinyl}\}$ amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 3-($N'-(3,4\text{-methylenedioxyphenylacetyl})\text{-L-alaninyl}$)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-($N'-(2\text{-methoxyphenoxyacetyl})\text{-L-alaninyl}$)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-($N'-(4\text{-isopropylphenoxyacetyl})\text{-L-alaninyl}$)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-($N'-(\text{ethoxyacetyl})\text{-L-alaninyl}$)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(4-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(4-ethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(2,5-dimethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(3,5-difluorobenzoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(o-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(3,3-diphenylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-phenoxypropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(indole-3-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-((4-methylphenoxy)acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(4-(hydroxymethyl)phenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(2-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3,4-dichlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4-fluorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

3-(N'-(methoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

5 (S)-3-(N'-(phenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

10 (S)-3-(N'-(2-phenoxybutyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

15 (S)-3-(N'-(3-methoxyphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(4-(trifluoromethyl)phenylacetyl)glycinyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

20 (S)-3-(N'-(4-butoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(3-(2-methoxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

25 (S)-3-(N'-(4-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

30 (S)-3-(N'-(isopropoxylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(1-phenyl-1H-tetrazole-5-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

35 (S)-3-(N'-(3-(3,4-methylenedioxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(3-cyclopentylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

40 (S)-3-(N'-(2-cyclopentene-1-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

45 (S)-3-(N'-(2-chloro-6-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-(N'-(cyclohexylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(2,5-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(pentafluorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,5-dimethylphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(4-chlorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-chlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(benzo[b]thiophene-3-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(benzoylformyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(3,5-dimethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(2,5-dimethylphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2,6-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(2,4-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(mesitylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(4-biphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,4-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(trans-styrylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(3-benzoylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(trans-3-hexenoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(heptanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(4-methylphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(3-(4-chlorophenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-phenylbutyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(4-(4-methoxyphenyl)butyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-methoxycarbonylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(4-phenylbutyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(benzylthio)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(3-methylpentanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(6-methoxycarbonylheptanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-indanylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(4-methoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-chlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(2-thiopheneacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(3-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(4-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(2,6-difluoromandelyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-methoxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(m-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-chlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(2-naphthylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-chlorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(3-methylphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(3,4-methylenedioxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-methoxyphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(4-isopropylphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(phenylmercaptoacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(4-ethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(2,5-dimethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(o-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,3-diphenylpropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(3-phenoxypropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(indole-3-acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(2-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-phenoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(4-fluorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(2,4-dichlorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-((methylthio)acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(4-fluoromandelyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-thionaphthenacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(methoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(ethoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(3-indolepropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(3-(2-chlorophenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(butyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(hexanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(5-phenylpentanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-nitrophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(3-(3-methoxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(5-methylhexanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(hydrocinnamyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(octanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(3-hydroxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(3-(4-hydroxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(3,4,5-trifluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(5-hydantoinacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(2-methyl-3-Benzofuranacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(cyclopropylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-methoxypropionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(5-(thienyl)pentanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(4-fluorophenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(3-(4-fluorophenoxy)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-norbornaneacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(2,3-difluoromandelyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(3-pentenoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-(2,4-dichlorophenoxy)butyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(2,3-dichlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(4-chlorobenzoyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(2-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(2-(4-cyanophenoxy)-2-methyl propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(2-nitrophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(4-(hydroxymethyl)phenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-fluoro-3-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(2,4,6-trifluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(4-fluoro-2-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-fluoro-4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(4-bromophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(4-fluorobenzoyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-((2-methylphenoxy)acetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(4-methoxyphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(phenylsulfonyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(2-methoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-bromophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(p-isopropylphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(4-pentenoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(4-hydroxyphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(4-oxopentanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2-hydroxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(3,4-dimethoxyphenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(4-methoxybenzoyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(thien-3-ylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(6-phenylhexanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(isovaleryl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(2,4,5-trifluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(1-adamantaneacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(cyclohexanepentanoyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(2-thiopheneacetyl)-L-phenylglycinyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-(trifluoromethyl)phenylacetyl)-L-phenylglycinyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(3,5-difluorophenylacetyl)-L-phenylglycinyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(3-tolylacetyl)-L-phenylglycinyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(3-fluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(3-bromophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3-chlorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(3,4-methylenedioxyphenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(phenylmercaptoacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(acetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-((methylthio)acetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(phenoxyacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(phenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 (S)-3-(N'-(cyclohexylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(2,5-difluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 (S)-3-(N'-(benzo[b]thiophene-3-acetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(benzoylformyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 (S)-3-(N'-(2,6-difluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 (S)-3-(N'-(2,4-difluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- (S)-3-(N'-(3,4-difluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 (S)-3-(N'-(butyryl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(heptanoyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 (S)-3-(N'-(4-(2-thienyl)butyryl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(5-methylhexanoyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 (S)-3-(N'-(hydrocinnamyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(cyclopentylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 (S)-3-(N'-(propionyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- (S)-3-(N'-(3,4,5-trifluorophenylacetyl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 (S)-3-(N'-(4-phenylbutyryl)-L-phenylglyciny)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(2-thiopheneacetyl)-L-alaniny)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(2-thiopheneacetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(2-thiopheneacetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(2-thiopheneacetyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(methylthio)acetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(methylthio)acetyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-(N'-(phenylacetyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(phenylacetyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(phenylacetyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(phenylacetyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(phenylacetyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(phenylacetyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(phenylacetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(phenylacetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(phenylacetyl)-L-alaninyl)-amino-)2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-(N'-(benzoylformyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(benzoylformyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(benzoylformyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(benzoylformyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(benzoylformyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(benzoylformyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(benzoylformyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(benzoylformyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(benzoylformyl)-L-alaninyl)-amino-)2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-(N'-(butyryl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(butyryl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(butyryl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(butyryl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(butyryl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(butyryl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(butyryl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(butyryl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(butyryl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(4-(2-thienyl)butyryl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(cyclopentylacetyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(3-(trifluoromethyl)butyryl)-L-alaninyl)-amino-)2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)-amino-)2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-(N'-(isovaleryl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(isovaleryl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(isovaleryl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one

- 3-(N'-(isovaleryl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(isovaleryl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(isovaleryl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(isovaleryl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(isovaleryl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(isovaleryl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-2,3-dihydro-5-phenyl-1-(4,4,4-trifluorobutyl)-1H-1,4-benzodiazepin-2-one

- 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-1-(2-oxo-2-phenylethyl)-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-1-methyl-2,3-dihydro-5-(2-thiazolyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-5-(2-thienyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(L-(+)-mandelyl)-L-alaninyl)amino-7-bromo-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-fluorobenzyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(benzyl)-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-*tert*-butylbenzyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-cyclohexylethyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethylbutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(1-methoxycarbonyl-1-phenylmethyl)-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-ethylbutyl)-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(cyclohexylmethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-phenylethyl)-1H-1,4-benzodiazepin-2-one

- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenylpropyl)-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-(N-phthalimidyl)ethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-biphenylmethyl)-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-((2-tetrahydrofuranyl)methyl)-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-(1,4-benzodioxanyl)methyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-(5-chlorobenzo[b]thienyl)methyl)-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethyl-2-oxo-propyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(5-benzofurazanylmethyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenoxypropyl)-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(6-(2-trifluoromethylquinolinyl)methyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methylbutyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-ethyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-pyridylmethyl)-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-oxo-2-(N-indolinyl)ethyl)-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-(3,5-dimethylisoxazolyl)methyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methoxyethyl)-1H-1,4-benzodiazepin-2-one

- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(benzyl)-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-*tert*-butylbenzyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-cyclohexylethyl)-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethylbutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(isopropyl)-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(1-methoxycarbonyl-1-phenylmethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-ethylbutyl)-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(cyclohexylmethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-phenylethyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenylpropyl)-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-(N-phthalimidyl)ethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-biphenylmethyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-(5-chlorobenzo[b]thienyl)methyl)-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(5-benzofurazanylmethyl)-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenoxypropyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(6-(2-trifluoromethylquinolinyl)methyl)-1H-1,4-benzodiazepin-2-one

5 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(cyclopropylmethyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methylbutyl)-1H-1,4-benzodiazepin-2-one

10 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-ethyl-1H-1,4-benzodiazepin-2-one

15 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-(3,5-dimethylisoxazolyl)methyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-propyl-1H-1,4-benzodiazepin-2-one

20 3-(N'-(cyclopentylacetyl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methoxyethyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(benzyl)-1H-1,4-benzodiazepin-2-one

25 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-*tert*-butylbenzyl)-1H-1,4-benzodiazepin-2-one

30 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-cyclohexylethyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethylbutyl)-1H-1,4-benzodiazepin-2-one

35 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(isopropyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(1-methoxycarbonyl-1-phenylmethyl)-1H-1,4-benzodiazepin-2-one

40 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-ethylbutyl)-1H-1,4-benzodiazepin-2-one

45 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(cyclohexylmethyl)-1H-1,4-benzodiazepin-2-one

3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenylpropyl)-1H-1,4-benzodiazepin-2-one

- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-biphenylmethyl)-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-(5-chlorobenzo[b]thienyl)methyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(5-benzofurazanylmethyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(3-phenoxypropyl)-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(6-(2-trifluoromethylquinolinyl)methyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(cyclopropylmethyl)-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methylbutyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(ethyl)-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(4-(3,5-dimethylisoxazolyl)methyl)-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(propyl)-1H-1,4-benzodiazepin-2-one
- 3-(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino-5-phenyl-2,3-dihydro-1-(2-methoxyethyl)-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(L-(+)-mandelyl)-L-alaninyl)-amino-)-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 (S)-3-(N'-(N-pyrrolidinylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-(N'-(2-chlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-(N'-(2-thiopheneacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-(N'-(3-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 3-(N'-(4-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 3-(N'-(3-(4-methoxyphenyl)propionyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 3-(N'-(m-tolylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-(N'-(3-fluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 3-(N'-(3-bromophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(4-chlorophenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-(N'-(2-naphthylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-(N'-(3-methylphenoxyacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(4-methoxyphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(2-thiopheneacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-bromophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(phenylmercaptoacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-ethoxyphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-((methylthio)acetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(cyclohexylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(pentafluorophenoxyacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(benzo[b]thiophene-3-acetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(2,4,6-trimethylphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(4-biphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3,4-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(5-methylhexanoyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-methoxycarbonylpropionyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(2,6-difluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(4-fluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(2,5-difluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(2,4,6-trifluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(4-fluoro-2-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(4-isopropylphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(beta-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(mandelyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(4-chloromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(isovaleryl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(3-methylthiopropionyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-nitrophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(D-3-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-methocyphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(2-thiopheneacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-bromophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(phenylmercaptoacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(4-ethoxyphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(cyclohexylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(pentafluorophenoxyacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(benzo[b]thiophene-3-acetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(2,4,6-trimethylphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(4-biphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(3,4-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-(2-thienyl)butyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(5-methylhexanoyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(2,6-difluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-fluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(2,5-difluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(2,4,6-trifluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(4-fluoro-2-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(4-isopropylphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(beta-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(mandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(4-chloromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(isovaleryl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-methylthiopropionyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-nitrophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(D-3-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-methoxyphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(2-thiopheneacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethylaminoethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(N"-acetyl-N"-phenylglyciny)l-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(phenylmercaptoacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(cyclohexylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(pentafluorophenoxyacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(benzo[b]thiophene-3-acetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(benzoylformyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3,4-difluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-(2-thienyl)butyryl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(5-methylhexanoyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(4-fluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[(N'-(2,5-difluoromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[(N'-(4,4,4-trifluorobutyryl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[(N'-(4-isopropylphenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[(N'-(beta-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[(N'-(mandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[(N'-(4-chloromandelyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[(N'-(isovaleryl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[(N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[(N'-(3-methylthiopropionyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[(N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(3-nitrophenylacetyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[(N'-(D-3-phenyllactyl)-L-alaninyl)amino]-2,3-dihydro-1-(2-N,N-diethyl aminoethyl)- 5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N-(3,5-difluorophenylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(3,5-difluorophenylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(3,5-difluorophenylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(3,5-difluorophenylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(3,5-difluorophenylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N-(3,5-difluorophenylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N-(3,5-difluorophenylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N-(3,5-difluorophenylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N-(3,5-difluorophenylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45 3-[N-(3,5-difluorophenylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N-(3,5-difluorophenylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(3,5-difluorophenylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(3,5-difluorophenylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(3,5-difluorophenylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(3,5-difluorophenylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N-(3,5-difluorophenylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(3,5-difluorophenylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N-(cyclopentylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N-(cyclopentylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N-(cyclopentylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45 3-[N-(cyclopentylacetyl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N-(cyclopentylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(cyclopentylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(cyclopentylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(cyclopentylacetyl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(cyclopentylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N-(cyclopentylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N-(cyclopentylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N-(cyclopentylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N-(cyclopentylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45 3-[N-(cyclopentylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N-(cyclopentylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(cyclopentylacetyl)-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-serinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(cyclopentylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(cyclopentylacetyl)-L-threoninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(cyclopentylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(cyclopentylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N-(cyclopentylacetyl)-L-tyrosinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N-(4,4,4-trifluorobutryl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N-(4,4,4-trifluorobutryl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N-(4,4,4-trifluorobutryl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-valinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45 3-[N-(4,4,4-trifluorobutryl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N-(4,4,4-trifluorobutryl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(4,4,4-trifluorobutryl)-L-norvalinyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(4,4,4-trifluorobutryl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-methioninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(4,4,4-trifluorobutryl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(4,4,4-trifluorobutryl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-phenylalaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N-(4,4,4-trifluorobutryl)-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N-(4,4,4-trifluorobutryl)-L-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N-(4,4,4-trifluorobutryl)-L-(2-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N-(4,4,4-trifluorobutryl)-L-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N-(4,4,4-trifluorobutryl)-L-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45

- 3-[N-(4,4,4-trifluorobutryl)-L-(3-thienyl)glycine]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N-(4,4,4-trifluorobutryl)-L-cyclohexylglycinyll]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N-(4,4,4-trifluorobutryl)-L-cyclohexylglycinyll]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N-(4,4,4-trifluorobutryl)-L-threoninyll]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N-(4,4,4-trifluorobutryl)-threoninyll]-amino-2,4-dioxo-1,5-bis-(methyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-(3,5-difluorophenylacetyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyll)amino-2,3-dihydro-1-ethyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyll]-amino-2,3-dihydro-1-methyl-5-(1-piperidinyll)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyll]-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(3,5-difluorophenylacetyl)-N'-methyl-L-alaninyll]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyll]-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-valinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-*tert*-leucinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(cyclopentyl- α -hydroxyacetyl)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(cyclopentyl- α -hydroxyacetyl)-L-valinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1,5-dimethyl-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-isobutyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(3,5-difluorophenyl- α -oxoacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-methylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3,5-difluorophenylacetyl)-L-valinyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(3,5-difluorophenylacetyl)-L-*tert*-leucinyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-isopropyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-cyclopropylmethyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(3,5-difluorophenyl- α -fluoroacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(3-methylbutyryl)-L-phenylglycinyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(3,5-difluorophenylacetyl)-L-phenylglycinyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(2-phenylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(3-methylbutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(2-phenylthioacetyl)-L-phenylglycinyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3-(4-methoxyphenyl)propionyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(3-bromophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-cyclohexylbutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-methoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-methyl-2-hydroxybutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-methyl-2-hydroxybutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,3-dimethylbutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

- 3-[N'-(thien-2-yl-acetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-bromophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(2-phenylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-ethoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(4-trifluoromethylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(3,5-di(trifluoromethyl)phenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-methylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(2-cyclohexylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(2,3,4,5,6-pentafluorophenoxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(thionaphth-3-ylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(2,4,6-trimethylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-phenylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3,4-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-(thien-2-yl)butyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(5-methylhexanoyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(2-methoxycarbonylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(2,6-difluorophenyl)- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-fluorophenyl)- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(2,5-difluorophenyl)- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(2,4,6-trifluorophenyl)acetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-trifluoromethyl-4-fluorophenyl)acetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(4,4,4-trifluorobutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-*iso*-propylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(3-phenyl-2-hydroxypropionyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(phenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-chlorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(3-methylbutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3-methylthiopropionyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-methyl-2-hydroxybutyryl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(3-nitrophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-methyl-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(4-methoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(2-thienylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(3-bromophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-phenylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(4-ethoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(4-trifluoromethylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-di-(trifluoromethyl)phenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(2-methylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(2-cyclomethylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2,3,4,5,6-pentafluorophenoxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(thionaphth-3-ylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(2,4,6-trimethylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-phenylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(3,4-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(4-(2-thienyl)butyryl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(5-methylhexanoyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(2-methoxycarbonylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(4-fluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(2,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(2,4,6-trifluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(2-trifluoromethyl-4-fluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(4-*iso*-propylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(3-phenyl-2-hydroxypropionyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(phenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-chlorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-methylbutyryl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(2,3,5-trifluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(3-methylthiopropionyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(3-methyl-2-hydroxybutyryl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(3-nitrophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(*tert*-butylcarbonylmethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-methoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(2-thienylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(3-bromophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(2-phenylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(4-ethoxyphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(2-methylthioacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-cyclohexylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(2,3,4,5,6-pentafluorophenoxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-thionaphth-3-ylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(2-phenyl-2-oxoacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2,4,6-trimethylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-((4-phenyl)phenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-((3,4-difluorophenyl)acetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-((4-(thien-2-yl)butyryl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 10 3-[N'-(5-methylhexanoyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-methoxycarbonylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 15 3-[N'-(2,6-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 20 3-[N'-(4-fluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 25 3-[N'-(4-hydroxymethylphenoxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 30 3-[N'-(2,4,6-trifluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(2-trifluoromethyl-4-fluorophenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 35 3-[N'-(4,4,4-trifluorobutyryl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 40 3-[N'-(4-*iso*-propylphenylacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 3-[N'-(3-phenyl-2-hydroxypropionyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 45 3-[N'-(phenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one

- 3-[N'-(4-chlorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,3-dihydro-1-(2-(N,N-diethylamino)ethyl)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one
- 5 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-3-thienylglyciny]amino-2,4-dioxo-1,5-bis(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,4-dioxo-1-phenyl-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-L-1H-imidazole[1,2-a]-6-phenyl-1,4-benzodiazepine
- 20 4-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-L-1H-imidazole[1,2-a]-2,4-dihydro-6-phenyl-1,4-benzodiazepine
- 25 4-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-L-4H[1,2,4]triazole[4,3-a]-6-phenyl-1,4-benzodiazepine
- 30 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-[N'-(3,5-difluorophenylacetyl)-(R)-2-thienylglyciny]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 40 3-[N'-(cyclopropylacetyl)-R-2-thienylglyciny]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 45 3-[N'-(cyclopentylacetyl)-R-2-thienylglyciny]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(cyclopentylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

- 3-[N'-(cyclopropylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 5 3-[N'-(3,5-difluorophenylacetyl)-S-2-phenylglycinyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 10 3-[N'-(cyclopentylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(cyclopentyl- α -hydroxyacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 15 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(3,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 20 3-[N'-(cyclopentylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(cyclopentyl- α -hydroxyacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 25 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 30 3-[N'-(cyclopentylacetyl)-L-alaninyl]amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 3-[N'-(cyclopentyl- α -hydroxyacetyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
- 35 3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one
- 40 5-{N'-(cyclopentylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-cyclopentylpropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(cyclohexylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5- $\{N'-(t\text{-butylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5- $\{N'-(\text{phenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3\text{-bromophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5- $\{N'-(3\text{-fluorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3\text{-chlorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5- $\{N'-(3\text{-(trifluoromethyl)phenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4\text{-fluorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5- $\{N'-(\text{hexanoyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(\text{heptanoyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5- $\{3,4\text{-difluorophenylacetyl}\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5- $\{N'-(\text{cyclopropylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2\text{-cyclopentene-1-acetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5- $\{N'-(3\text{-cyclohexylpropionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(\text{isovaleryl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5- $\{N'-(\text{citronellyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5- $\{N'-(3\text{-benzoylpropionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(2-chlorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(4-pentenoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(valeryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(2-thiophenecetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-(2-thienyl)butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(4-(4-nitrophenyl)butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2,4-difluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(2,6-difluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-isopropylphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(1-adamantaneacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(5-cyclohexanepentanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-((methylthio)acetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(2-thiophenepentanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2-norbornaneacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(3,5-difluorophenylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(3,5-difluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(3,5-difluorophenylacetyl)-3-cyclopropylalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(3,5-difluorophenylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-difluorophenylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(3,5-difluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(cyclohexylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(cyclopropylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(isovaleryl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(3-(trifluoromethyl)phenylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(3,4-difluorophenylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2,4-difluorophenylacetyl)-4-ethylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3-fluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(cyclopentylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(cyclohexylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(cyclopropylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2-thiopheneacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(isovaleryl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(3-(trifluoromethyl)phenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(4-fluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,4-difluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(2,4-difluorophenylacetyl)-4-methylnorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-fluorophenylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(cyclopentylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(cyclohexylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(cyclopropylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(isovaleryl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(4-fluorophenylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3,4-difluorophenylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2,4-difluorophenylacetyl)-4-cyclohexylhomoalaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(3-fluorophenylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(cyclopentylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(cyclohexylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(cyclopropylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45

- 5-{N'-(isovaleryl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(3-(trifluoromethyl)phenylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(4-fluorophenylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(3,4-difluorophenylacetyl)-6-fluoronorleucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(4-methoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(3-(4-methoxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(1-naphthylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(3,4-methylenedioxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(hydrocinnamyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(octanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(3-hydroxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(4-methylphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(4-chlorophenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-phenylbutyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(4-hydroxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(3,4,5-trifluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(4-(4-methoxyphenyl)butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(3-(methoxycarbonyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(4-phenylbutyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(3-(benzylthio)-propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(3-methylpentanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(7-carbomethoxyheptanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(2-indanylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(5-carbomethoxypentanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(2-methyl-3-Benzofuranacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-methoxypropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(4-fluorophenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(4-fluorophenoxy)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-pentenoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-(2,4-dichlorophenoxy)butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5- $\{N'-(2,3\text{-dichlorophenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5- $\{N'-(3-(4\text{-chlorobenzoyl})\text{propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5- $\{N'-(4'\text{-fluorosuccinanilyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5- $\{N'-(N\text{-(diphenylmethyl)glutaramyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5- $\{N'-(2\text{-fluorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5- $\{N'-(\text{cyanoacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5- $\{N'-(\text{succinanilyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5- $\{N'-(2,4\text{-dichlorophenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5- $\{N'-(2\text{-nitrophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5- $\{N'-(\beta\text{-propylhydrocinnamyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3-(2,4\text{-dimethylbenzoyl})\text{propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2\text{-fluoro-3-(trifluoromethyl)phenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2,4,6\text{-trifluorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4\text{-fluoro-2-(trifluoromethyl)phenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2\text{-fluoro-4-(trifluoromethyl)phenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4\text{-hydroxyphenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5- $\{N'-(4\text{-methoxyphenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5- $\{N'-(2\text{-methoxyphenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2\text{-bromophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5- $\{N'-(4\text{-benzyloxyphenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4\text{-hydroxyphenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5- $\{N'-(\text{levulinyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2\text{-hydroxyphenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5- $\{N'-(3,4\text{-dimethoxyphenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3-(4\text{-methoxybenzoyl})\text{propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5- $\{N'-(3-(4\text{-phenylbenzoyl})\text{propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5- $\{N'-(3\text{-hydroxyphenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(N\text{-acetyl-N-phenylglyciny})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5- $\{N'-(\text{thiophene-3-acetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(6\text{-phenylhexanoyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5- $\{N'-(4\text{-cyclohexanebutyryl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5- $\{N'-(2,3,5\text{-trifluorophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(2,4,5-trifluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(vinylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-methylthiopropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(3-nitrophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(N-tert-butylsuccinamyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(4-bromophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(3-(4-fluorobenzoyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(o-chlorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(p-tolylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(m-tolylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3,4-dichlorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-chlorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(3-methylphenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(4-isopropylphenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-phenoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(phenylmercaptoacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(4-ethoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(2,5-dimethoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(o-tolylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(3,3-diphenylpropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-phenoxypropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(4-(trifluoromethyl)phenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-((4-methylphenoxy)acetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(2-phenoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-phenoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(3,4-dichlorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(4-fluorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,4,5-trimethoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(2,4-dichlorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(4-thianaphthenacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(methoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(ethoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(phenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(3-methoxyphenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(4-butoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(3-(2-methoxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(N,N-dimethylsuccinamyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-(3,4-methylenedioxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(2-chloro-6-fluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2,5-difluorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(2,3,4,5,6-pentafluorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-bis(trifluoromethyl)phenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3,5-dimethylphenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(4-chlorophenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3-chlorophenoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(benzo[b]thiophene-3-acetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-dimethoxyphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(2,5-dimethylphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(mesitylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(4-biphenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(N-(tert-butoxycarbonyl)-3-aminopropionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(trans-styrylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(4-acetamidobutyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(3-(2-chlorophenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(trans-3-hexenoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(5-phenylvaleryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3-(3-methoxyphenyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(4-chloro-beta-methylhydrocinnamyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(3-(trifluoromethyl)butyryl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(alpha-naphthoxyacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(3-(4-phenoxybenzoyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(3-(2-trifluoromethylbenzoyl)propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(3-benzoylamino-3-phenyl-propionyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5- $\{N'-(4-(\text{hydroxyimino})\text{pentanoyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5- $\{N'-(4'\text{-methylglutaranilyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-((4-(4\text{-ethyl-phenoxy})\text{-phenoxy})\text{-acetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5- $\{N'-(3\text{-benzoyl-3-phenylpropionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4-(\text{hydroxymethyl})\text{phenoxyacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5- $\{N'-(4,4,4\text{-trifluorobutyryl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3\text{-isobutyrylamino-3-phenyl-propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5- $\{N'-((2\text{-methylphenoxy})\text{acetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(3\text{-(phenylsulfonyl)propionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5- $\{N'-(4\text{-nitrophenylacetyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5- $\{N'-(3\text{-ethoxypropionyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(2,3\text{-difluoromandelyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5- $\{N'-(2,6\text{-difluoromandelyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5- $\{N'-(4\text{-fluoromandelyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5- $\{N'-(2,5\text{-difluoromandelyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5- $\{N'-(\text{beta-phenyllactyl})\text{-L-alaninyl}\}$ -amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

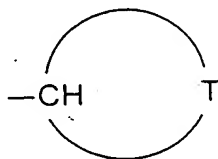
- 5-{N'-(mandelyl)}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(p-chloromandelyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(L-alpha-hydroxyisocaproyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(4-bromomandelyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(L-(+)-lactyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(D-3-phenyllactyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(5-methylhexanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(3,5-difluorophenylacetyl)-L-methioninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-difluorophenylacetyl)-L-2-phenylglycinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(3,5-difluorophenylacetyl)-L-leucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(3,5-difluorophenylacetyl)-L-2-cyclohexylglycinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(3,5-difluorophenylacetyl)-L-threoninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(3,5-difluorophenylacetyl)-L-alpha-(2-thienyl)glycinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(2-thiopheneacetyl)-L-methioninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(2-thiopheneacetyl)-L-2-phenylglycinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(2-thiopheneacetyl)-L-leucinyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

- 5-{N'-(2-thiopheneacetyl)-L-2-cyclohexylglyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-{N'-(2-thiopheneacetyl)-L-threoniny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-{N'-(2-thiopheneacetyl)-L-alpha-(2-thienyl)glyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-{N'-(isovaleryl)-L-methioniny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-{N'-(isovaleryl)-L-2-phenylglyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-{N'-(isovaleryl)-L-leuciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-{N'-(isovaleryl)-L-2-cyclohexylglyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-{N'-(isovaleryl)-L-threoniny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-{N'-(isovaleryl)-L-alpha-(2-thienyl)glyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-{N'-(phenylacetyl)-L-methioniny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(phenylacetyl)-L-2-phenylglyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(phenylacetyl)-L-leuciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(phenylacetyl)-L-2-cyclohexylglyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(phenylacetyl)-L-threoniny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-{N'-(phenylacetyl)-L-alpha-(2-thienyl)glyciny}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Preferred cyclic groups defined by W and $-C(H)_pC(=X)-$ include cycloalkyl, lactone, lactam, benzazepinone, dibenzazepinone and benzodiazepine groups. In one preferred embodiment, the cyclic group defined by W and $-C(H)_pC(=X)-$, forms a cycloalkyl group of the formula:

5

10

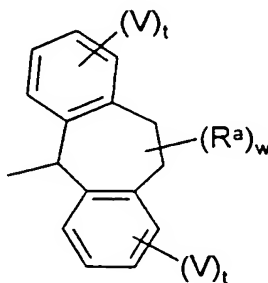


15

20 wherein T is selected from the group consisting of alkylene and substituted alkylene.

A preferred cycloalkyl group is represented by the formula:

25



30

wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected

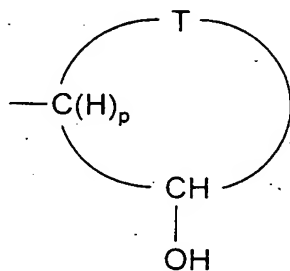
35

from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; t is an integer from 0 to 4; and w is an integer from 0 to 3.

5 Preferably t is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

In another preferred embodiment, the cyclic group defined by W, together with $-C(H)_pC(=X)-$ is a ring of the formula:

10

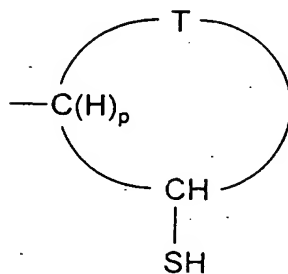


15

20

or

25



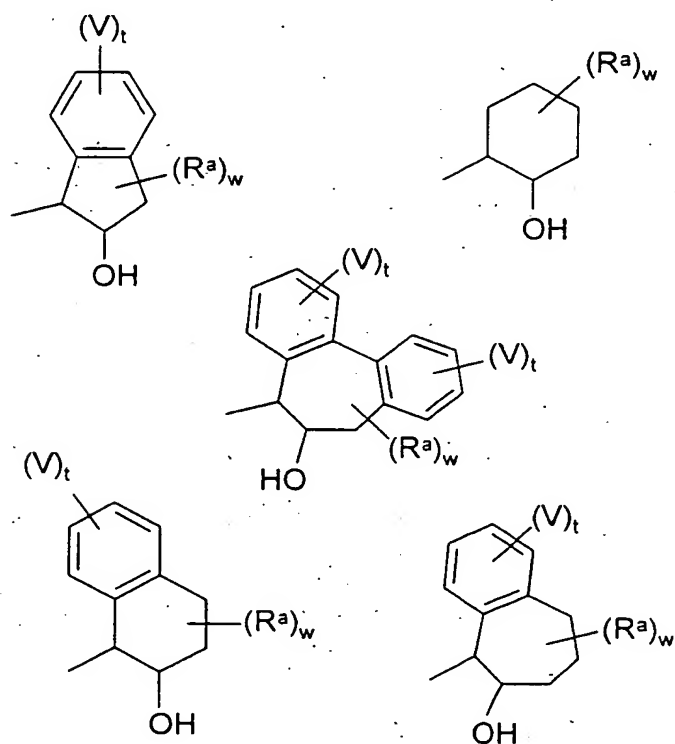
30

35

wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$

where Z is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently
 5 alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

10 Particularly preferred alcohol or thiol substituted groups include



wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl,
 30 substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl,

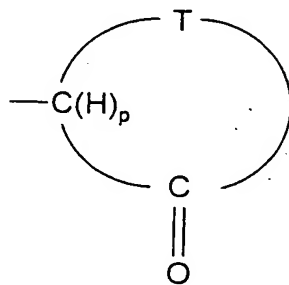
thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; t is an integer from 0 to 4; and w is an integer from 0 to 3.

5

Preferably t is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

Yet another preferred embodiment of the cyclic group defined by W,
10 together with $-C(H)_pC(=X)-$, is a ring of the formula:

15

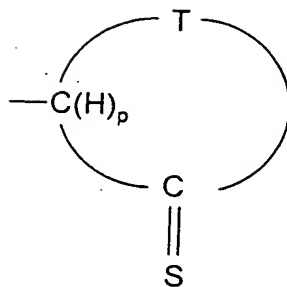


20

25

or

30



35

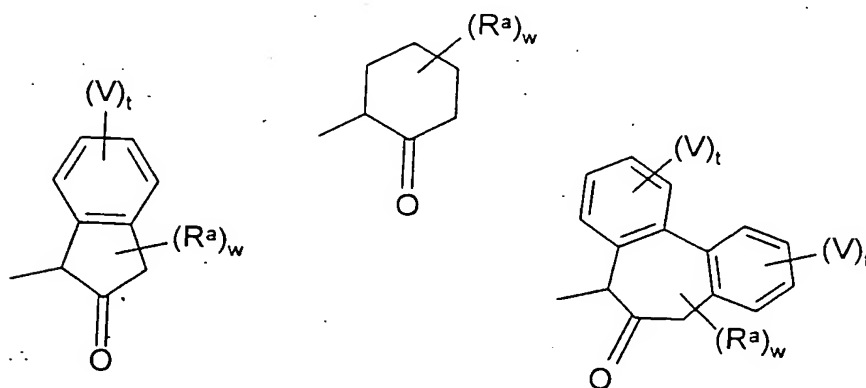
40

wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred cyclic ketone and thioketone groups include:

15

20



25

wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy,

30

amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; t is an integer from 0 to 4; and w is an integer from 0 to 3.

5 Preferably t is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

In another preferred embodiment, the cyclic group defined by W , together with $-C(H)_pC(=X)-$, forms a ring of the formula:

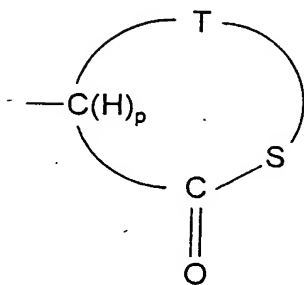
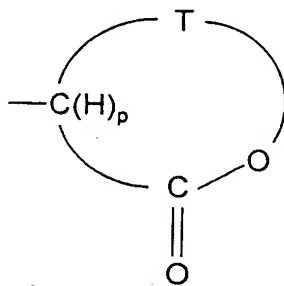
10

15

20

25

30



5

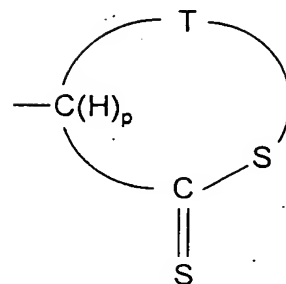
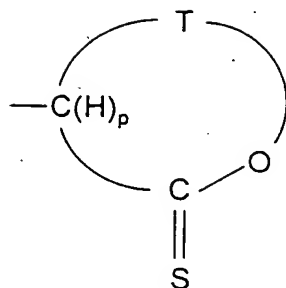
10

or

15

20

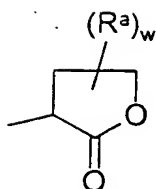
25



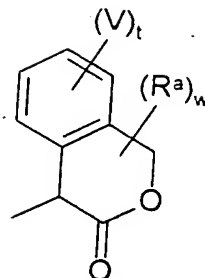
wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred lactone and thiolactone groups include:

5



and



10

wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; *t* is an integer from 0 to 4; and *w* is an integer from 0 to 3.

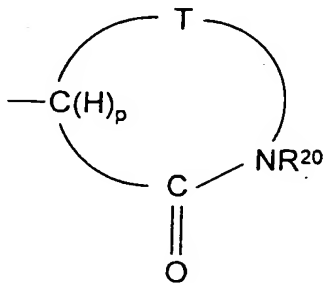
15

Preferably *t* is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

20

In another preferred embodiment, the cyclic group defined by W and -C(H)_pC(=X)-, forms a lactam ring of the formula:

25



30

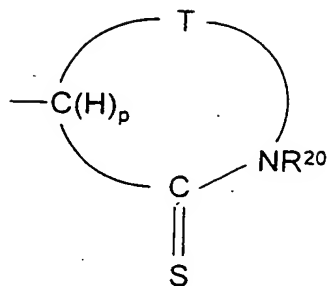
35

or a thiolactam ring of the formula:

5

10

15



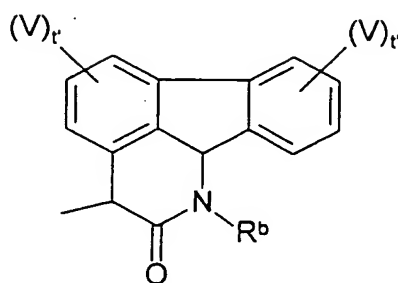
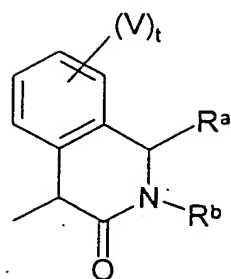
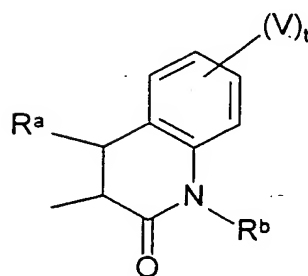
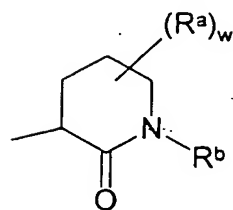
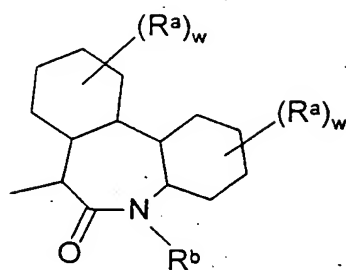
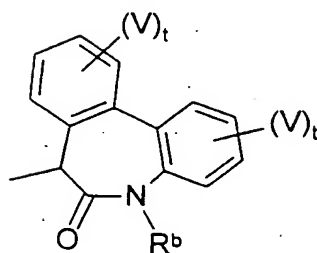
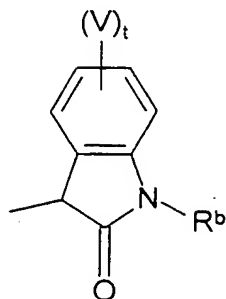
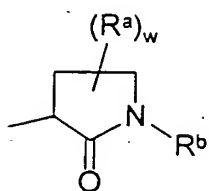
20

25

30

wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred lactam and thiolactam groups include:

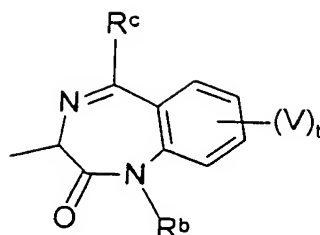
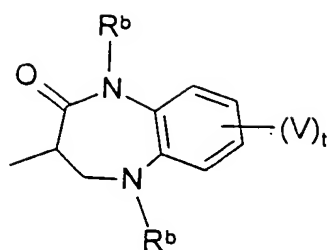


"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

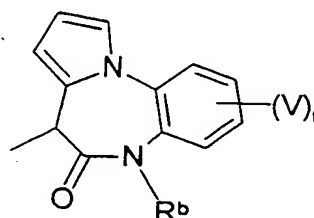
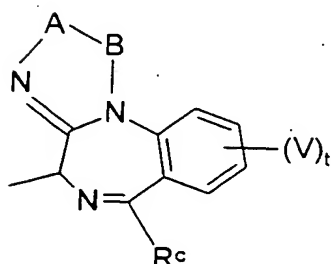
"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic; and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, and where each R can be joined to form, together with the nitrogen atom, a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted

5



10



wherein A-B is selected from the group consisting of alkylene, alkenylene, substituted alkylene, substituted alkenylene and -N=CH-; Q' is oxygen or sulfur; each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; R^b is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, heteroaryl, heterocyclic, and the like; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclic, cycloalkyl, and substituted cycloalkyl; *t* is an integer from 0 to 4; *t'* is an integer from 0 to 3; and *w* is an integer from 0 to 3.

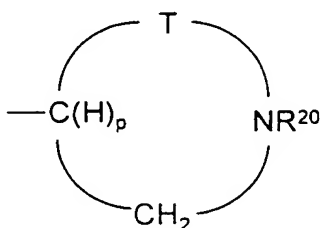
Preferably *t* is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

30

In another preferred embodiment, the cyclic group defined by W, together with $-C(H)_pC(=X)-$, forms a ring of the formula:

5

10



15

wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$, where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

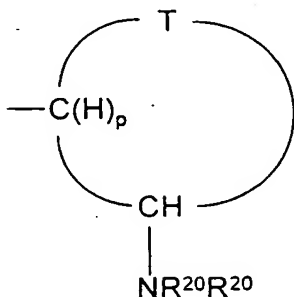
20

25

A still further preferred embodiment is directed to a ring group defined by W, together with $-C(H)_pC(=X)-$, of the formula:

30

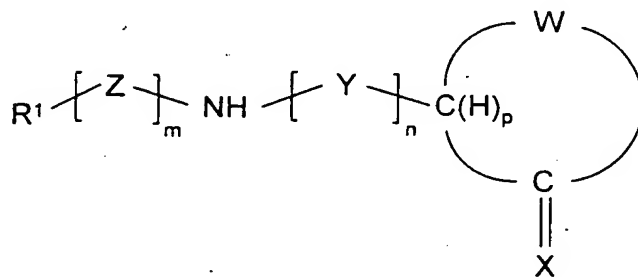
35



wherein p is zero or one, T is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

This invention also provides for novel pharmaceutical compositions comprising a pharmaceutically inert carrier and a compound of the formula I above.

Still further, this invention provides for novel compounds of the formula I:



I

wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

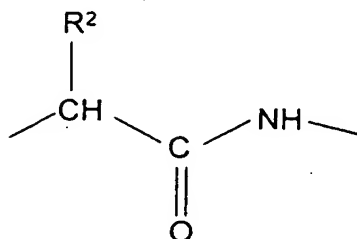
5 W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring
10 structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted
15 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

 X is selected from the group consisting of oxo ($=O$), thiooxo ($=S$), hydroxyl ($-H$, $-OH$), thiol (H , $-SH$) and hydro (H , H);

 Y is represented by the formula:

25

30



35

wherein each R^2 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

5 Z is represented by the formula $-T-CX'X''C(O)-$ where T is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur, $-NR^5$ where R^5 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

X' is hydrogen, hydroxy or fluoro,

X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

10 m is an integer equal to 0 or 1;

n is an integer equal to 0, 1 or 2;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to Y and when p is one, the ring is saturated at the carbon atom of ring

15 attachment to Y,

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, m is 1, n is 1, and p is 1, then W, together with $>CH$ and $>C=X$, does not form a 2-(S)-indanol group;

20 B. when R^1 is phenyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, m is 1, n is 1, and p is 1, then W, together with $>CH$ and $>C=X$, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R^1 is phenyl, Z is $-CH_2C(O)-$, m is 1, n is 0, and p is 1, then W, together with $>CH$ and $>C=X$, does not form a gammabutyrolactone group or a 5,5-dimethyl-gammabutyrolactone group;

25

D. when R^1 is phenyl, Z is $-CH_2C(O)-$, m is 1, n is 0, and p is 1, then W, together with $>CH$ and $>C=X$, does not form a ϵ -caprolactam group;

E. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z is $-CH_2C(O)-$, m is 1, n is 1, and p is 1, then W, together with $>CH$ and $>C=X$, does not form an N-methylcaprolactam group;

30

F. when R^1 is 4-chlorobenzoyl- CH_2 -, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})$ -, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

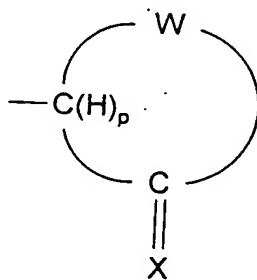
G. when R^1 is 2-phenylphenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})$ -, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

H. when R^1 is $\text{CH}_3\text{OC}(\text{O})\text{CH}_2$ -, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})$ -, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form an 2,3-dihydro-1-(*t*-butyl $\text{C}(\text{O})\text{CH}_2$ -)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $\text{CH}_3\text{OC}(\text{O})\text{CH}_2$ -, 4- HOCH_2 -phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH_3S -, R^2 is $-\text{CH}_3$, Z is $-\text{CH}_2\text{C}(\text{O})$ -, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a 2,3-dihydro-1-(*N,N*-diethylamino- CH_2CH_2 -)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

J. when R^1 is 2,6-difluorophenyl, R^2 is $-\text{CH}_3$, Z is $-\text{CH}(\text{OH})\text{C}(\text{O})$ -, m is 1, n is 1, and p is 1, then W , together with $>\text{CH}$ and $>\text{C}=\text{X}$, does not form a 2,3-dihydro-1-(*N,N*-diethylamino- CH_2CH_2 -)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one,

K. when m is 1 and n is 1, then

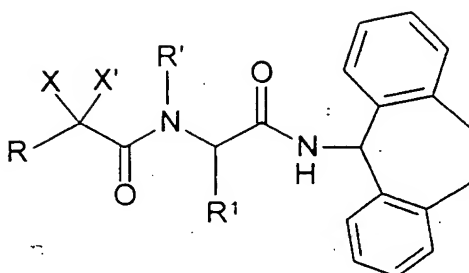


does not equal cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

5 The products of this invention include mixtures of R,S enantiomers at any stereochemical center. Preferably, however, when a chiral product is desired, the chiral product corresponds to the L-amino acid derivative. In the formulas set forth herein, a mixture of R,S enantiomers at the stereochemical center is sometimes indicated by a squiggly line as per convention. Othertimes, no stereochemical designation is made at the stereochemical center and this also infers that a mixture of enantiomers is present.

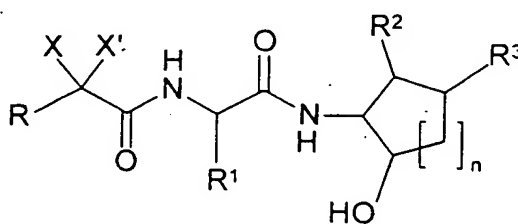
10 Preferred compounds described herein include those set forth in the tables below:

TABLE 1-1



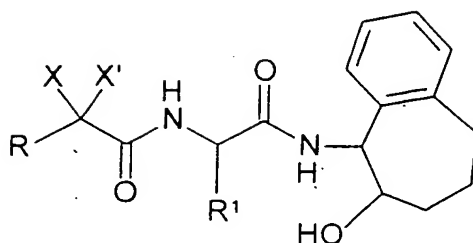
Ex.	R	R'	X'/X''	R'
1-1	3,5-di-F- ϕ -	H	H,H	-CH ₃

TABLE 2-1



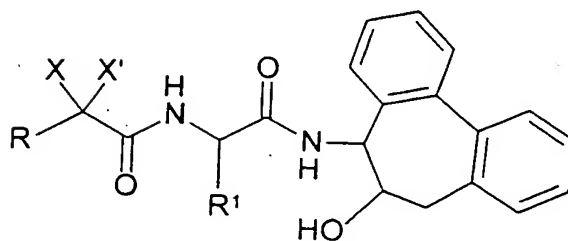
Ex.	R	X'/X''	R'	R ² /R ³	n
2-1	3,5-di-F- ϕ -	H,H	-CH ₃	forms a fused phenyl ring	1
2-3	3,5-di-F- ϕ -	H,H	-CH ₃	forms a fused phenyl ring	1
2-3	3,5-di-F- ϕ -	H,H	-CH ₃	forms a fused phenyl ring	1
2-4	3,5-di-F- ϕ -	H,H	-CH ₃	H,H	2
2-5	3,5-di-F- ϕ -	H,H	-CH ₃	forms a fused phenyl ring	2
2-6	3,5-di-F- ϕ -	H,H	-CH ₃	forms a fused phenyl ring	3

TABLE 2-2



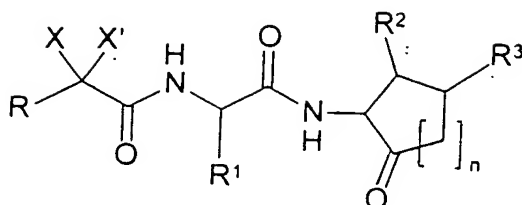
Ex.	R	X'/X''	R ¹
2-6	3,5-di-F-φ-	H,H	-CH ₃

TABLE 2-3



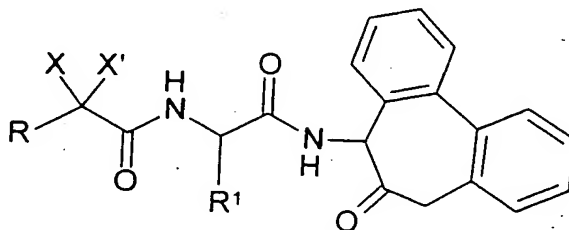
Ex.	R	X'/X''	R ¹
2-7	3,5-di-F-φ-	H,H	-CH ₃

TABLE 3-1



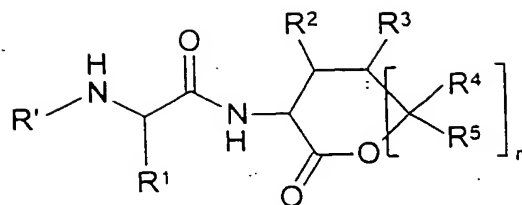
Ex.	R	X'/X''	R ¹	R ² /R ³	n
3-1	3,5-di-F-φ-	H,H	-CH ₃	forms a fused phenyl ring	1
3-2	φ-	H,H	-CH ₃	forms a fused phenyl ring	2

TABLE 3-2



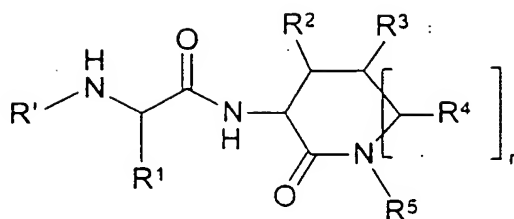
Ex.	R	X'/X''	R ¹
3-3	3,5-di-F-φ-	H,H	-CH ₃

TABLE 4-1



Ex.	R'	R ¹	R ² /R ³	R ⁴	R ⁵	n
4-1	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H.H	--	--	0
4-2	3,4-di-Cl- ϕ -	-CH ₃	H.H	--	--	0
4-3	cyclopentyl-CH ₂ C(O)-	-CH ₃	forms a fused phenyl ring	-CH ₃	-CH ₃	1
4-4	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	forms a fused phenyl ring	-CH ₃	-CH ₃	1

TABLE 5-1

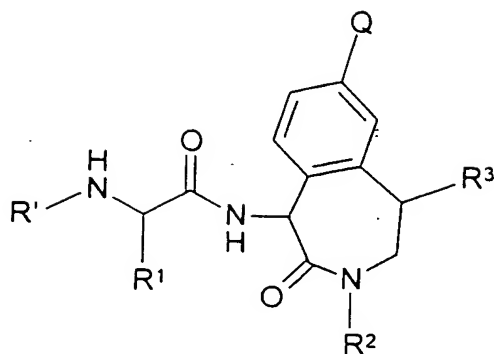


Ex.	R'	R ¹	R ²	R ³	R ⁴ /R ^{4'} (R ^{4'} when n = 2)	R ⁵	n
5-1	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	H	H	-	H	0
5-2	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	H	H	H	H	1
5-3	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	H	H	H	-CH ₂ φ	1
5-4	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₃	H	H,H	H	2
5-5	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	H	R ² /R ³ = fused phenyl ring	-	H	1
5-6	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	H	R ² /R ³ = fused phenyl ring	-	-CH ₂ φ	1
5-7	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	-	H	H	1
5-8	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	-	H	-CH ₂ φ	1
5-9	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	-	-CH ₃	H	1
5-10	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	-	-φ	H	1
5-11	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring with 3-F subs.	-	H	H	1

Ex.	R'	R ¹	R ²	R ³	R ⁴ /R ^{4'} (R ^{4'} when n = 2)	R ⁵	n
5-12	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring with 4-F subs.	--	H	H	1
5-14	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	H	-CH ₂ CH ₂ ϕ	1
5-14	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	H	-CH ₃	1
5-15	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring with 3- ϕ subs.	--	H	H	1
5-16	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring with 4- ϕ subs.	--	H	H	1
5-17	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ /R ⁴ together with the pendent atoms form (9-amino- fluorene-1- yl)glycine δ -lactam	--	--	H	1
5-18	ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	H	2
5-19	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	H	2
5-20	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	-CH ₂ ϕ	2
5-21	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	2-methoxy- ethoxy	2
5-22	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	ethyl	2
5-23	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	ethyl	H,H	H	2
5-24	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	ethyl	H,H	H	2
5-25	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H, benzyl	H	2
5-26	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = ethylene	H	H	-CH ₂ ϕ	1
5-27	cyclopentyl-CH ₂ C(O)-	-CH ₃	H	H	H,H	-CH ₂ ϕ	2
5-28	cyclopentyl-CH ₂ C(O)-	ϕ	H	H	H,H	-CH ₂ ϕ	2

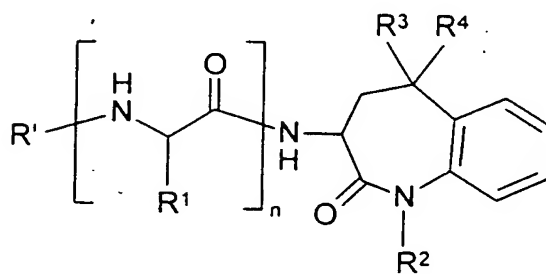
Ex.	R'	R ¹	R ²	R ³	R ³ /R ⁴ (R ⁴ when n = 2)	R ⁵	n
5-29	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H	-CH ₂ CH ₂ ϕ	2
5-30	cyclopentyl-CH ₂ C(O)-	- ϕ	H	H	H,H	-CH ₂ CH ₂ ϕ	2
5-31	3,4-di-Cl- ϕ -	-CH ₃	H	H	H,H	H	2
5-32	cyclopropyl-CH ₂ C(O)-	- ϕ	H	H	H,H	-CH ₃	2
5-33	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	H	H,H, H,H	H	4
5-34	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ¹ = fused phenyl ring with 4-benzyl subs.	H	H	H	1
5-35	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	-CH ₂ ϕ	H	1
5-36	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	- ϕ	-CH ₃	1
5-37	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	pyrid- 2-yl	H	1
5-38	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	pyrid- 3-yl	H	1
5-39	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	pyrid- 4-yl	H	1
5-40	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	R ² /R ³ = fused phenyl ring	--	--	-CH ₃	0
5-41	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	- ϕ (trans)	R ³ /R ⁴ = fused phenyl ring	--	-CH ₃	1
5-42	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	- ϕ (cis)	R ³ /R ⁴ = fused phenyl ring	--	-CH ₃	1
5-43	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	- ϕ (trans)	R ³ /R ⁴ = fused phenyl ring	--	H	1

TABLE 6-1



Ex.	R'	R ¹	R ²	R ³	Q
6-1	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃	H	H
6-2	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₂ CH ₃	H	F
6-16	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	ϕ	H

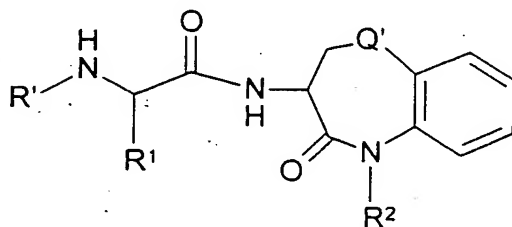
TABLE 6-2



Ex.	R'	n	R ¹	R ²	R ³	R ⁴
6-3	3,5-di-F- ϕ -CH ₂ C(O)-	0	--	-CH ₂ CH ₃	-CH ₃	-CH ₃
6-4	3,5-di-F- ϕ -CH ₂ C(O)-	1	-CH ₃	H	H	H
6-5	3,5-di-F- ϕ -CH ₂ C(O)-	1	-CH ₃	-CH ₂ ϕ	H	H

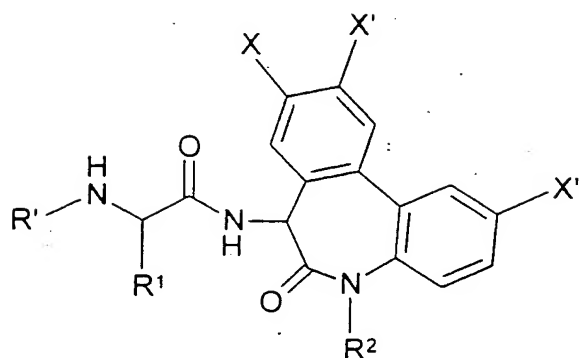
Ex.	R'	n	R ¹	R ²	R ³	R ⁴
6-6	cyclopentyl-CH ₂ C(O)-	0	--	-CH ₂ CH ₃	-CH ₃	-CH ₃
6-7	3,5-di-F-φ-CH ₂ C(O)-	1	-CH ₃	-CH ₃	H	H
6-8	3,5-di-F-φ-CH ₂ C(O)-	0	-CH ₃	-CH ₃	-CH ₃	H
6-9	3,5-di-F-φ-CH ₂ C(O)-	1	-CH ₃	-CH ₃	-CH ₃	H
6-13	3,5-di-F-φ-CH ₂ C(O)-	1	-CH ₃	H	-CH ₃	-CH ₃
6-14	3,5-di-F-φ-CH ₂ C(O)-	1	-CH ₃	-CH ₃	-CH ₃	-CH ₃
6-15	3,5-di-F-φ-CH(OH)C(O)-	1	-CH ₃	-CH ₃	-CH ₃	-CH ₃
6-17	3,5-di-F-φ-CH ₂ C(O)-	1	-CH ₃	-CH ₂ CH ₃	-CH ₃	-CH ₃

TABLE 6-3



Ex.	R'	R ¹	R ²	Q'
6-10	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₃	O
6-11	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₂ CH ₃	O
6-12	3,5-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₃	S

TABLE 7-1

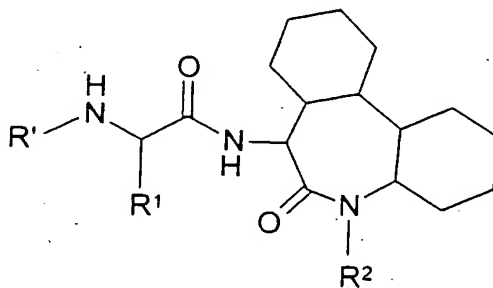


Ex.	R'	R¹	R²	X	X'	X''
7-1	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₃	H	H	H
7-2	3,5-di-F- ϕ - CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	H
7-3	3,5-di-F- ϕ - C(O)C(O)-	-CH ₃	-CH ₃	H	H	H
7-4	3,5-di-F- ϕ - CH ₂ C(O)-	-CH(CH ₃) ₂	-CH ₃	H	H	H
7-5	3,5-di-F- ϕ - CH ₂ C(O)-	-C(CH ₃) ₃	-CH ₃	H	H	H
7-6	3,5-di-F- ϕ - CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	H	H	H
7-7	3,5-di-F- ϕ - CH(OH)C(O)-	-C(CH ₃) ₃	-CH ₃	H	H	H
7-8	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₂ C(O)OCH ₃	H	H	H
7-9	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₂ C(O)OH	H	H	H
7-10	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₂ C(O)C(CH ₃) ₃	H	H	H
7-11	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₂ -C(O)- morpholin-4-yl	H	H	H
7-12	(CH ₃) ₂ CH- CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	H
7-13	cyclopentyl- CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	H	H	H
7-14	(CH ₃) ₂ C- CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	H

Ex.	R'	R ¹	R ²	X	X'	X''
7-15	cyclopentyl- CH(OH)C(O)-	-C(CH ₃) ₃	-CH ₃	H	H	H
7-16	cyclopentyl- CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	H
7-17	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	H	H	H	H
7-18	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	-CH ₂ CH(CH ₃) ₂	H	H	H
7-19	(CH ₃) ₂ CH- CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	H	H	H
7-20	(CH ₃) ₂ C- CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	H
7-21	2-(φ)-φ-	-CH ₃	-CH ₃	H	H	H
7-22	4-φ- furazan-3-yl	-CH ₃	-CH ₃	H	H	H
7-30	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	-(CH ₂) ₄ φ	H	H	H
7-25	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	-CH ₂ -cyclopropyl	H	H	H
7-26	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	-CH ₂ CF ₃	H	H	H
7-27	3,5-di-F-φ- CH ₂ C(O)-	-CH ₃	cyclohexyl	H	H	H
7-28	3,5-di-F-φ- CH(OH)C(O)-	-CH ₃	-CH ₃	F	H	H
7-29	3,5-di-F-φ- CH(OH)C(O)-	-CH ₃	-CH ₃	H	H	F
7-30	3,5-di-F-φ- CH(OH)C(O)-	-CH ₃	-CH ₃	H	F	H
7-31	3,5-di-F-φ- CH(OH)C(O)-	-CH ₃	-CH ₂ -cyclopropyl	H	H	H
7-32	3,5-di-F-φ- CH(OH)C(O)-	-CH ₃	-(CH ₂) ₄ φ	H	H	H
7-33	3,5-di-F-φ- CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₂ -cyclopropyl	H	H	H
7-34	3,5-di-F-φ- CH(OH)C(O)-	-CH(CH ₃) ₂	-(CH ₂) ₄ φ	H	H	H
7-35	3,5-di-F-φ- CH(OH)C(O)-	-CH(CH ₃) ₂	hexyl	H	H	H
7-36	3,5-di-F-φ- CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	H	F	H

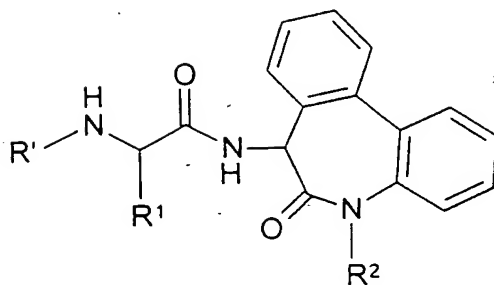
Ex.	R'	R ¹	R ²	X	X'	X''
7-37	3,5-di-F- ϕ - CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	H	H	F
7-38	3,5-di-F- ϕ - CH(OH)C(O)-	-CH(CH ₃) ₂	-CH ₃	F	H	H
7-39	3,4-di-Cl- ϕ -	- ϕ	-CH ₃	H	H	H

TABLE 7-2



Ex.	R'	R ¹	R ²
7-23	3,5-di-F- ϕ - CH ₂ C(O)-	-CH ₃	-CH ₃

TABLE 7C-1



Ex.	R'	R¹	R²
7C-1	cyclopentylCH₂C(O)-	-CH₃	-CH₃
7C-2	cyclopentylCH₂CH₂C(O)-	-CH₃	-CH₃
7C-3	cyclohexylCH₂C(O)-	-CH₃	-CH₃
7C-4	(CH₃)₃CCH₂C(O)-	-CH₃	-CH₃
7C-5	φ-CH₂C(O)-	-CH₃	-CH₃
7C-6	3-Br-φ-CH₂C(O)-	-CH₃	-CH₃
7C-7	3-F-φ-CH₂C(O)-	-CH₃	-CH₃
7C-8	3-Cl-φ-CH₂C(O)-	-CH₃	-CH₃
7C-9	3-CF₃-φ-CH₂C(O)-	-CH₃	-CH₃
7C-10	4-F-φ-CH₂C(O)-	-CH₃	-CH₃
7C-11	CH₃(CH₂)₄C(O)-	-CH₃	-CH₃
7C-12	CH₃(CH₂)₃C(O)-	-CH₃	-CH₃
7C-13	3,4-di-F-φ-CH₂C(O)-	-CH₃	-CH₃
7C-14	cyclopropyl-CH₂C(O)-	-CH₃	-CH₃
7C-15	cyclopent-1-enyl-CH₂C(O)-	-CH₃	-CH₃
7C-16	cyclohexyl-CH₂CH₂C(O)-	-CH₃	-CH₃
7C-17	(CH₃)₂CHCH₂C(O)-	-CH₃	-CH₃
7C-18	(CH₃)₂CH=CH(CH₂)₂CH(CH₃)- CH₂C(O)-	-CH₃	-CH₃
7C-19	φC(O)CH₂-CH₂C(O)-	-CH₃	-CH₃
7C-20	2-Cl-φ-CH₂C(O)-	-CH₃	-CH₃
7C-21	CH₂=CHCH₂-CH₂C(O)-	-CH₃	-CH₃

Ex.	R'	R ¹	R ²
7C-22	CH ₃ (CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-23	thien-2-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-24	thien-2-yl-(CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-25	4-NO ₂ -φ-(CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-26	2,4-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-27	2,6-di-F-φ-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-28	4-(CH ₃) ₂ CH-φ-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-29	adamantan-1-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-30	cyclohexyl-(CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-31	CH ₃ SCH ₂ C(O)-	-CH ₃	-CH ₃
7C-32	thien-2-yl-(CH ₂) ₄ C(O)-	-CH ₃	-CH ₃
7C-33	norbornan-2-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-34	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-35	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-36	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ -cyclopropyl	-CH ₃
7C-37	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ CH ₂ -cyclohexyl	-CH ₃
7C-38	3,5-di-F-φ-CH ₂ C(O)-	-(CH ₂) ₃ CH ₂ F	-CH ₃
7C-39	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-40	cyclohexyl-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-41	cyclopropyl-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-42	(CH ₃) ₂ CHCH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-43	3-CF ₃ -φ-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-44	3,4-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-45	2,4-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₂ CH ₃) ₂	-CH ₃
7C-46	3-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-47	cyclopentyl-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-48	cyclohexyl-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-49	cyclopropyl-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-50	thien-2-yl-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-51	(CH ₃) ₂ CHCH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-52	3-CF ₃ -φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-53	4-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-54	3,4-di-F-φ-CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃

Ex.	R'	R ¹	R ²
7C-55	2,4-di-F- ϕ -CH ₂ C(O)-	-CH ₂ CH(CH ₃)CH ₂ CH ₃	-CH ₃
7C-56	3-F- ϕ -CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-57	cyclopentyl-CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-58	cyclohexyl-CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-59	cyclopropyl-CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-60	(CH ₃) ₂ CHCH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-61	4-F- ϕ -CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-62	3,4-F- ϕ -CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-63	2,4-F- ϕ -CH ₂ C(O)-	-CH ₂ CH ₂ cyclohexyl	-CH ₃
7C-64	3-F- ϕ -CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-65	cyclopentyl-CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-66	cyclohexyl-CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-67	cyclopropyl-CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-68	(CH ₃) ₂ CHCH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-69	3-CF ₃ - ϕ -CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-70	4-F- ϕ -CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-71	3,4-F- ϕ -CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-72	2,4-F- ϕ -CH ₂ C(O)-	-(CH ₂) ₅ CH ₂ F	-CH ₃
7C-73	4-CH ₃ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-74	4-CH ₃ O- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-75	naphth-1-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-76	3,4-methylenedioxy- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-77	ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-78	CH ₃ (CH ₂) ₆ C(O)-	-CH ₃	-CH ₃
7C-79	3-HO- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-80	4-CH ₃ - ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-81	4-Cl- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-82	CH ₃ CH(ϕ)CH ₂ C(O)-	-CH ₃	-CH ₃
7C-83	4-HO- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-84	3,4,5-tri-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-85	4-CH ₃ O- ϕ -CH ₂ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-86	CH ₃ OC(O)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-87	ϕ -CH ₂ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃

Ex.	R'	R ¹	R ²
7C-88	$\phi\text{-CH}_2\text{-S-CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-89	$\text{CH}_3\text{CH}_2\text{CH(CH}_3\text{)CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-90	$\text{CH}_3\text{OC(O)(CH}_2\text{)}_6\text{C(O)-}$	-CH_3	-CH_3
7C-91	indan-2-yl- $\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-92	$\text{CH}_3\text{OC(O)(CH}_2\text{)}_4\text{C(O)-}$	-CH_3	-CH_3
7C-93	(2-methylbenzofuran-3-yl) $\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-94	$\text{CH}_3\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-95	$\text{CH}_3\text{OCH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-96	4-F- $\phi\text{-CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-97	4-F- $\phi\text{-OCH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-99	$\text{CH}_3\text{CH=CHCH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-100	2,4-di-Cl- $\phi\text{-O-(CH}_2\text{)}_3\text{C(O)-}$	-CH_3	-CH_3
7C-101	2,3-di-Cl- $\phi\text{-O-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-102	4-Cl- $\phi\text{C(O)-CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-103	4-F- $\phi\text{-NHC(O)CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-104	$(\phi)_2\text{CHNHC(O)CH}_2\text{CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-105	2-F- $\phi\text{-CH}_2\text{-C(O)-}$	-CH_3	-CH_3
7C-107	$\phi\text{-NHC(O)CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-108	2,4-di-Cl- $\phi\text{-O-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-109	2-NO ₂ - $\phi\text{-CH}_2\text{-C(O)-}$	-CH_3	-CH_3
7C-110	$\text{CH}_3(\text{CH}_2)_2\text{CH}(\phi)\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-111	2,4-di-CH ₃ - $\phi\text{-C(O)(CH}_2\text{)}_2\text{C(O)-}$	-CH_3	-CH_3
7C-112	2-F-3-CF ₃ - $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-113	2,4,6-tri-F- $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-114	4-F-2-CF ₃ - $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-115	2-F-4-CF ₃ - $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-116	4-HO- $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-117	4-CH ₃ O- $\phi\text{-O-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-118	2-CH ₃ O- $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-119	2-Br- $\phi\text{-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-120	4-($\phi\text{-CH}_2\text{O-})\phi\text{-O-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-121	4-HO- $\phi\text{-O-CH}_2\text{C(O)-}$	-CH_3	-CH_3
7C-122	$\text{CH}_3\text{C(O)CH}_2\text{CH}_2\text{C(O)-}$	-CH_3	-CH_3

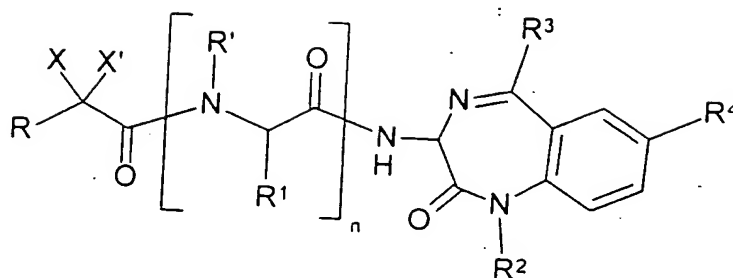
Ex.	R'	R'	R'
7C-123	2-HO- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-124	3,4-di-CH ₃ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-125	4-CH ₃ O- ϕ (CO)-CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-126	ϕ (CO)-CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-127	3-HO- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-128	CH ₃ C(O)N(ϕ)CH ₂ C(O)-	-CH ₃	-CH ₃
7C-129	thien-3-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-130	ϕ -(CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-131	cyclohexyl-(CH ₂) ₃ C(O)-	-CH ₃	-CH ₃
7C-132	2,3,5-tri-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-133	2,4,5-tri-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-134	CH ₂ =CHCH ₂ C(O)-	-CH ₃	-CH ₃
7C-135	CH ₃ S(CH ₂) ₂ C(O)-	-CH ₃	-CH ₃
7C-136	3-NO ₂ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-137	(CH ₃) ₃ CNHC(O)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-138	4-Br- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-139	4-F- ϕ C(O)-CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-140	2-Cl- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-141	4-CH ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-142	3-CH ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-143	3,4-di-Cl- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-144	4-Cl- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-145	3-CH ₃ - ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-146	4-(CH ₃) ₂ CH- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-147	4-(ϕ -O)- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-148	ϕ SCH ₂ C(O)-	-CH ₃	-CH ₃
7C-149	4-C ₂ H ₅ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-150	2,5-di-CH ₃ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-151	2-CH ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-152	(ϕ) ₂ CHCH ₂ C(O)-	-CH ₃	-CH ₃
7C-153	ϕ OCH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-154	4-CF ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-155	4-CH ₃ - ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃

Ex.	R'	R ¹	R ²
7C-156	2-(ϕ -O)- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-157	3-(ϕ -O)- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-158	3,4-di-Cl- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-159	4-F- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-160	3,4,5-tri-CH ₃ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-161	2,4-di-Cl- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-162	thianaphthen-4-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-163	CH ₃ OCH ₂ C(O)-	-CH ₃	-CH ₃
7C-164	C ₂ H ₅ OCH ₂ C(O)-	-CH ₃	-CH ₃
7C-165	ϕ OCH ₂ C(O)-	-CH ₃	-CH ₃
7C-166	3-CH ₃ O- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-167	4-C ₄ H ₉ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-168	2-CH ₃ O- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-169	(CH ₃) ₂ NC(O)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-170	3,4-methylenedioxy- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-171	2-Cl-6-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-172	2,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-173	2,3,4,5,6-penta-F- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-174	3,5-di-CF ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-175	3,5-di-CH ₃ - ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-176	4-Cl- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-177	3-Cl- ϕ -O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-178	benzo[b]thien-3-yl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-179	3,5-di-CH ₃ O- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-180	2,5-di-CH ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-181	2,4,6-tri-CH ₃ - ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-182	4-(ϕ)- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₃
7C-183	(CH ₃) ₂ COC(O)NH(CH ₃) ₂ C(O)-	-CH ₃	-CH ₃
7C-184	<i>trans</i> -styryl-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-185	H ₂ NC(O)(CH ₃) ₂ C(O)-	-CH ₃	-CH ₃
7C-186	2-Cl- ϕ -CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-187	CH ₃ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃

Ex.	R'	R ¹	R ²
7C-188	CH ₃ CH ₂ CH=CHCH ₂ C(O)- (trans)	-CH ₃	-CH ₃
7C-189	φ(CH ₂) ₂ C(O)-	-CH ₃	-CH ₃
7C-190	3-CH ₃ O-φ-CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-191	4-Cl-φ-CH(CH ₃)CH ₂ C(O)-	-CH ₃	-CH ₃
7C-192	CH ₃ CH(CF ₃)CH ₂ C(O)-	-CH ₃	-CH ₃
7C-194	naphthalen-1-yl-O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-196	2-(CF ₃)-φ-C(O)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-197	φC(O)NHCH(φ)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-198	CH ₃ CH(=NHOH)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-199	4-CH ₃ -φ-NHC(O)CH ₂ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-200	4-(C ₂ H ₅ -φ-O)φ-O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-201	φC(O)CH(φ)CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-202	4-(HOCH ₂)-φ-O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-203	CF ₃ (CH ₂) ₂ C(O)-	-CH ₃	-CH ₃
7C-204	(CH ₃) ₂ CHC(O)NHCH(φ)CH ₂ C(O)-	-CH ₃	-CH ₃
7C-205	2-CH ₃ -φ-O-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-206	φSO ₂ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-207	4-NO ₂ -φ-CH ₂ C(O)-	-CH ₃	-CH ₃
7C-208	C ₂ H ₅ OCH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-209	2,3-di-F-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-210	2,6-di-F-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-211	4-F-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-212	2,5-di-F-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-213	φ-CH ₂ CH(OH)C(O)-	-CH ₃	-CH ₃
7C-217	φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-215	4-Cl-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-216	(CH ₃) ₂ CHCH ₂ CH(OH)C(O)-	-CH ₃	-CH ₃
7C-217	4-Br-φ-CH(OH)C(O)-	-CH ₃	-CH ₃
7C-218	CH ₃ CH(OH)C(O)-	-CH ₃	-CH ₃
7C-219	φ-CH ₂ CH(OH)C(O)-	-CH ₃	-CH ₃
7C-220	(CH ₃) ₂ CHCH ₂ CH ₂ CH ₂ C(O)-	-CH ₃	-CH ₃
7C-221	3,5-di-F-φ-CH ₂ C(O)-	-CH ₂ CH ₂ SCH ₃	-CH ₃

Ex.	R'	R ¹	R ²
7-C222	3,5-di-F- ϕ -CH ₂ C(O)-	ϕ	-CH ₃
7-C223	3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₂ CH(CH ₃) ₂	-CH ₃
7-C224	3,5-di-F- ϕ -CH ₂ C(O)-	cyclohexyl	-CH ₃
7-C225	3,5-di-F- ϕ -CH ₂ C(O)-	-CH(OH)CH ₃	-CH ₃
7-C226	3,5-di-F- ϕ -CH ₂ C(O)-	thien-2-yl	-CH ₃
7-C227	thien-2-yl-CH ₂ C(O)-	-CH ₂ CH ₂ SCH ₃	-CH ₃
7-C228	thien-2-yl-CH ₂ C(O)-	ϕ	-CH ₃
7-C229	thien-2-yl-CH ₂ C(O)-	-CH ₂ CH(CH ₃) ₂	-CH ₃
7-C230	thien-2-yl-CH ₂ C(O)-	cyclohexyl	-CH ₃
7-C231	thien-2-yl-CH ₂ C(O)-	-CH(OH)CH ₃	-CH ₃
7-C232	thien-2-yl-CH ₂ C(O)-	thien-2-yl	-CH ₃
7-C233	(CH ₃) ₂ CHCH ₂ C(O)-	-CH ₂ CH ₂ SCH ₃	-CH ₃
7-C234	(CH ₃) ₂ CHCH ₂ C(O)-	ϕ	-CH ₃
7-C235	(CH ₃) ₂ CHCH ₂ C(O)-	-CH ₂ CH(CH ₃) ₂	-CH ₃
7-C236	(CH ₃) ₂ CHCH ₂ C(O)-	cyclohexyl	-CH ₃
7-C237	(CH ₃) ₂ CHCH ₂ C(O)-	-CH(OH)CH ₃	-CH ₃
7-C238	(CH ₃) ₂ CHCH ₂ C(O)-	thien-2-yl	-CH ₃
7-C239	ϕ -CH ₂ C(O)-	-CH ₂ CH ₂ SCH ₃	-CH ₃
7-C240	ϕ -CH ₂ C(O)-	ϕ	-CH ₃
7-C241	ϕ -CH ₂ C(O)-	-CH ₂ CH(CH ₃) ₂	-CH ₃
7-C242	ϕ -CH ₂ C(O)-	cyclohexyl	-CH ₃
7-C243	ϕ -CH ₂ C(O)-	-CH(OH)CH ₃	-CH ₃
7-C244	ϕ -CH ₂ C(O)-	thien-2-yl	-CH ₃

TABLE 8-1



$R^2 = 1 \text{ position}; R^3 = 5 \text{ position}; R^4 = 7 \text{ position}$

Ex.	R	R'	X'/X''	R'	R ²	R ³	R ⁴	n
8-1	3,5-di-F-φ-	-	H,H	--	-CH ₃	-φ	H	0
8-2	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₂ CH ₃	-φ	H	1
8-3	3,5-di-F-φ-	H	H,H	-CH ₃	H	-φ	H	1
8-4	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	piperidin-1-yl	H	1
8-5	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	-φ	Cl	1
8-6	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	2-F-φ-	Br	1
8-7	3,5-di-F-φ-	-CH ₃	H,H	-CH ₃	-CH ₃	-φ	H	1
8-8	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	2-Cl-φ-	Cl	1
8-9	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	cyclohexyl	H	1
8-10	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	-φ	NO ₂	1
8-11	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	2-F-φ-	H	1
8-12	3,5-di-F-φ-	H	OH,H	-CH(CH ₃) ₂	-CH ₃	-φ	H	1
8-13	3,5-di-F-φ-	H	OH,H	-C(CH ₃) ₃	-CH ₃	-φ	H	1
8-14	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	3-F-φ-	H	1
8-15	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	4-F-φ-	H	1
8-16	cyclopentyl	H	OH,H	-CH ₃	-CH ₃	-φ	H	1
8-17	cyclopentyl	H	OH,H	-CH(CH ₃) ₂	-CH ₃	-φ	H	1
8-18	3,5-di-F-φ-	H	H,H	-CH ₃	-CH ₃	-CH ₃	H	1

Ex.	R	R'	X'/X"	R ¹	R ²	R ³	R ⁴	n
8-19	3,5-di-F-φ-	H	H.H	-CH ₃	CH ₂ CH(CH ₃) ₂	-φ	H	1
8-20	3,5-di-F-φ-	H	OH.H	-CH ₃	-CH ₃	-φ	H	1
8-21	3,5-di-F-φ-	H	=O	-CH ₃	-CH ₃	-φ	H	1
8-22	CH ₃ S-	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-23	3,5-di-F-φ-	H	H.H	-CH(CH ₃) ₂	-CH ₃	-φ	H	1
8-24	3,5-di-F-φ-	H	H.H	-C(CH ₃) ₃	-CH ₃	-φ	H	1
8-25	3,5-di-F-φ-	H	H.H	-CH ₃	-CH(CH ₃) ₂	-φ	H	1
8-26	3,5-di-F-φ-	H	H.H	-CH ₃	1-cyclopropyl-methyl	-φ	H	1
8-27	3,5-di-F-φ-	H	F.H	-CH ₃	-CH ₃	-φ	H	1
8-28	3,5-di-F-φ-	H	H.H	-CH ₃	-CH ₂ CH ₂ CH ₃	-φ	H	1
8-29	(CH ₃) ₂ CH-	H	H.H	-φ	-CH ₃	-φ	H	1
8-30	3,5-di-F-φ-	H	H.H	-φ	-CH ₃	-φ	H	1
8-31	φ-S-	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-32	(CH ₃) ₂ CH-	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-33	φ-S-	H	H.H	-φ	-CH ₃	-φ	H	1
8-34	4-CH ₃ O-φ-CH ₃ -	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-35	3-Br-φ-	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-36	cyclohexyl-CH ₂ CH ₂ -	H	H.H	-CH ₃	-CH ₃	-φ	H	1
8-37	4-CH ₃ O-φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-38	(CH ₃) ₂ CH-	H	OH.H	-CH ₃	-CH ₃	-φ	H	1
8-39	(CH ₃) ₂ CH-	H	OH.H	-CH(CH ₃) ₂	-CH ₃	-φ	H	1
8-40	(CH ₃) ₃ C-	H	OH.H	-CH ₃	-CH ₃	-φ	H	1
8-41	2-thienyl	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-42	3,5-di-F-φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-43	3-Br-φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-44	φ-S-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-45	4-CH ₃ CH ₂ O-φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-46	4-CF ₃ -φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-47	3,5-di-CF ₃ -φ-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-48	CH ₃ S-	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-49	cyclohexyl	H	H.H	-CH ₃	-CH ₃	2-pyridyl	H	1

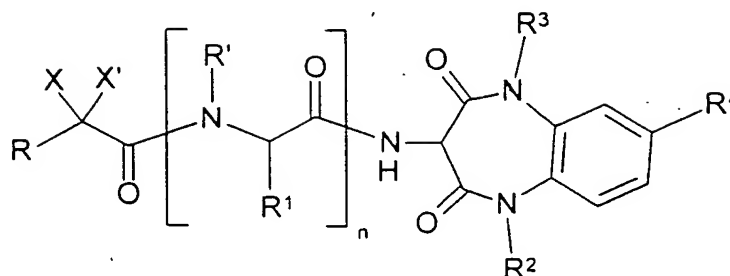
Ex.	R	R'	X'/X''	R ¹	R ²	R ³	R ⁴	n
8-50	2,3,4,5,6-penta-F- ϕ -O-	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-51	3-thio-naphthalyl	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-52	2,4,6-tri-CH ₃ - ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-53	(4- ϕ)- ϕ	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-54	3,4-di-F- ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-55	2-thienyl-CH ₂ CH ₂ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-56	(CH ₃) ₂ CH-CH ₂ CH ₂ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-57	CH ₃ OC(O)CH ₂ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-60	2,6-di-F- ϕ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-61	4-F- ϕ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-62	2,5-di-F- ϕ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-63	2,4,6-tri-F- ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-64	2-CF ₃ -4-F- ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-65	CF ₃ CH ₂ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-66	(4-(CH ₃) ₂ CH-) ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-67	ϕ -CH ₂ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-68	ϕ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-69	4-Cl- ϕ -	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-70	(CH ₃) ₂ CH-	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-71	2,3,5-tri-F- ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-72	CH ₃ S-CH ₂ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-73	(CH ₃) ₂ CH-	H	OH,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-74	3-NO ₂ - ϕ -	H	H,H	-CH ₃	-CH ₃	2-pyridyl	H	1
8-75	4-CH ₃ O- ϕ -	H	H,H	-CH ₃	(CH ₃) ₂ CC(O)-CH ₂ -	2-pyridyl	H	1
8-76	2-thienyl	H	H,H	-CH ₃	(CH ₃) ₂ CC(O)-CH ₂ -	2-pyridyl	H	1
8-77	3,5-di-F- ϕ -	H	H,H	-CH ₃	(CH ₃) ₂ CC(O)-CH ₂ -	2-pyridyl	H	1
8-78	3-Br- ϕ -	H	H,H	-CH ₃	(CH ₃) ₂ CC(O)-CH ₂ -	2-pyridyl	H	1

Ex.	R	R'	X'/X''	R ¹	R ²	R ³	R ⁴	n
8-79	ϕ -S-	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-80	4-CH ₃ CH ₂ O- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-81	4-CF ₃ - ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-82	3,5-di-CF ₃ - ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-83	CH ₃ S-	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-84	cyclohexyl	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-85	2,3,4,5,6-penta-F- ϕ -O-	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-86	3-thio-naphthalyl	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-87	2,4,6-tri-CH ₃ - ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-88	(4- ϕ)- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-89	3,4-di-F- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-90	thien-2-yl-CH ₂ CH ₂ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-91	(CH ₃) ₂ CH(CH ₃) ₂ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-92	CH ₃ OC(O)CH ₂ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-93	2,6-di-F- ϕ -	H	OH,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-96	4-F- ϕ -	H	OH,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-97	2,5-di-F- ϕ -	H	OH,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-99	2,4,6-tri-F- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-99	2-CF ₃ -4-F- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-100	CF ₃ CH ₂ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1
8-101	4-(CH ₃) ₂ CH- ϕ -	H	H,H	-CH ₃	(CH ₃) ₃ CC(O)-CH ₂ -	2-pyridyl	H	1

Ex.	R	R'	X'/X''	R ¹	R ²	R ³	R ⁴	n
8-102	$\phi\text{CH}_2\text{-}$	H	OH.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-103	$\phi\text{-}$	H	OH.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-104	4-Cl- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-105	$(\text{CH}_3)_2\text{CH-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-106	2,3,5-tri-F- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-107	$\text{CH}_3\text{S-CH}_2\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-108	$(\text{CH}_3)_2\text{CH-}$	H	OH.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-109	3-NO ₂ - $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3)_3\text{CC}(\text{O})\text{-CH}_2\text{-}$	2-pyridyl	H	1
8-110	4-CH ₃ O- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-111	2-thienyl	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-112	3,5-di-F- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-113	3-Br- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-114	$\phi\text{-S-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-115	(4-CH ₃ CH ₂ O)- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-116	$\text{CH}_3\text{S-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-117	cyclohexyl	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-118	2,3,4,5,6-penta-F- $\phi\text{-O-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-119	3-thio-naphthalyl	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-120	$\phi\text{-}$	H	=O	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-121	2,4,6-tri-CH ₃ - $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1
8-122	(4- $\phi\text{-}$)- $\phi\text{-}$	H	H.H	$-\text{CH}_3$	$(\text{CH}_3\text{CH}_2)_2\text{N-CH}_2\text{CH}_2\text{-}$	2-pyridyl	H	1

Ex.	R	R'	X'/X''	R ¹	R ²	R ³	R ⁴	n
8-123	3,4-di-F- ϕ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-124	thien-2-yl-CH ₂ CH ₂ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-125	(CH ₃) ₂ CH(CH ₂) ₂ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-126	CH ₃ OC(O)CH ₂ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-129	2,6-di-F- ϕ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-130	4-F- ϕ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-131	2,5-di-F- ϕ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-132	4-HOCH ₂ - ϕ -O-	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-133	2,4,6-tri-F- ϕ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-134	2-CF ₃ -4-F- ϕ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-135	CF ₃ CH ₂ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-136	(CH ₃) ₂ CH- ϕ -	H	H,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-137	ϕ CH ₂ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-138	ϕ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-139	4-Cl- ϕ -	H	OH,H	-CH ₃	(CH ₃ CH ₂) ₂ N-CH ₂ CH ₂ -	2-pyridyl	H	1
8-166	3,5-di-F- ϕ -	H	H,H	-CH ₃	-CH ₃	- ϕ	H	1

TABLE 8-2

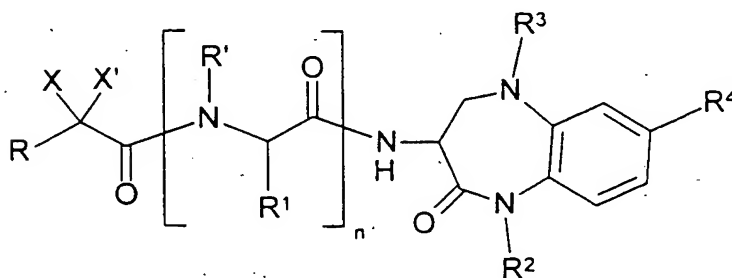


$R^2 = 1 \text{ position}; R^3 = 5 \text{ position}; R^4 = 7 \text{ position}$

Ex.	R	X'/X''	R'	R ¹	R ²	R ³	R ⁴	n
8-140	3,5-di-F-φ-	OH,H	H	thien-3-yl	-CH ₂ C(CH ₃) ₃	-CH ₂ C(CH ₃) ₃	H	1
8-141	3,5-di-F-φ-	OH,H	H	-CH ₃	-φ	-CH ₃	H	1
8-142	3,5-di-F-φ-	OH,H	H	-CH ₃	-CH ₃	-φ	H	1
8-146	3,5-di-F-φ-	H,H	H	-CH ₃	-CH(CH ₃) ₂	-CH(CH ₃) ₂	H	1
8-147	3,5-di-F-φ-	H,H	H	2-thienyl	-CH(CH ₃) ₂	-CH(CH ₃) ₂	H	1
8-148	cyclopropyl	H,H	H	2-thienyl	-CH(CH ₃) ₂	-CH(CH ₃) ₂	H	1
8-149	cyclopentyl	H,H	H	2-thienyl	-CH(CH ₃) ₂	-CH(CH ₃) ₂	H	1
8-150	3,5-di-F-φ-	H,H	H	-CH ₃	-CH ₃	-CH ₃	H	1
8-151	3,5-di-F-φ-	OH,H	H	-CH ₃	-CH ₃	-CH ₃	H	1
8-152	3,5-di-F-φ-	H,H	H	-CH ₃	-CH ₂ CH(CH ₃) ₂	-CH ₂ CH(CH ₃) ₂	H	1
8-153	cyclopentyl	H,H	H	-CH ₃	-CH ₂ CH(CH ₃) ₂	-CH ₂ CH(CH ₃) ₂	H	1
8-154	cyclopropyl	H,H	H	-CH ₃	-CH ₂ CH(CH ₃) ₂	-CH ₂ CH(CH ₃) ₂	H	1
8-155	3,5-di-F-φ-	H,H	H	-φ	-CH ₂ CH(CH ₃) ₂	-CH ₂ CH(CH ₃) ₂	H	1
8-156	3,5-di-F-φ-	H,H	H	-CH ₃	1-cyclopropyl-methyl	1-cyclopropyl-methyl	H	1
8-157	cyclopentyl	H,H	H	-CH ₃	1-cyclopropyl-methyl	1-cyclopropyl-methyl	H	1
8-158	cyclopentyl	OH,H	H	-CH ₃	1-cyclopropyl-methyl	1-cyclopropyl-methyl	H	1
8-159	3,5-di-F-φ-	H,H	H	-CH ₃	-CH ₂ C(CH ₃) ₃	-CH ₂ C(CH ₃) ₃	H	1
8-160	3,5-di-F-φ-	OH,H	H	-CH ₃	-CH ₂ C(CH ₃) ₃	-CH ₂ C(CH ₃) ₃	H	1

Ex.	R	X'/X''	R'	R ¹	R ²	R ³	R ⁴	n
8-161	cyclopentyl	H.H	H	-CH ₃	-CH ₂ C(CH ₃) ₃	-CH ₂ C(CH ₃) ₃	H	1
8-162	cyclopentyl	OH.H	H	-CH ₃	-CH ₂ C(CH ₃) ₃	-CH ₂ C(CH ₃) ₃	H	1
8-163	3,5-di-F-φ-	H.H	H	-CH ₃	-φ	-φ	H	1
8-164	cyclopentyl	H.H	H	-CH ₃	-φ	-φ	H	1
8-165	cyclopentyl	OH.H	H	-CH ₃	-φ	-φ	H	1

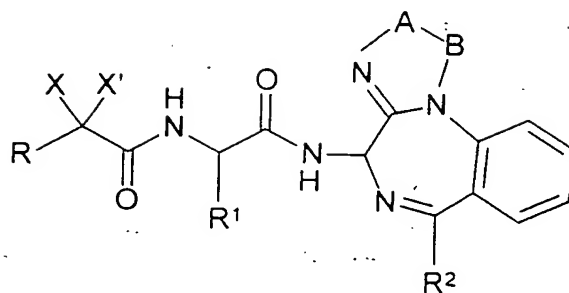
TABLE 8-3



R² = 1 position; R³ = 5 position; R⁴ = 7 position

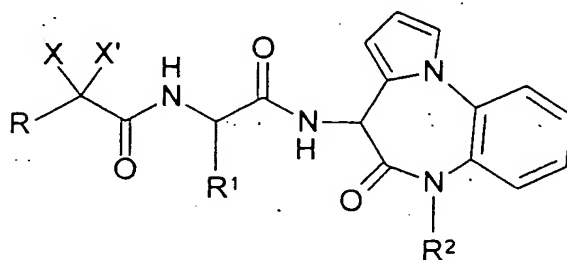
Ex.	R	X'/X''	R'	R ¹	R ²	R ³	R ⁴	n
8-142	3,5-di-F-φ-	OH.H	H	-CH ₃	-CH ₃	-φ	H	1

TABLE 8-4



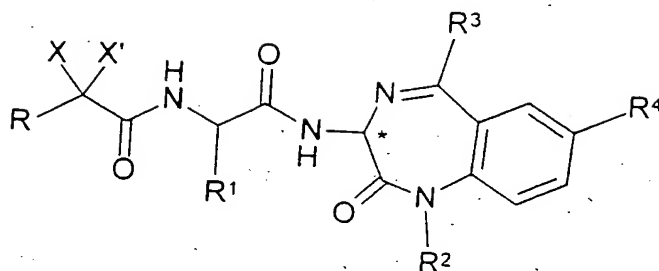
Ex.	R	X'/X''	R¹	R²	A-B
8-143	3,5-di-F-φ-	H,H	-CH₃	-φ	-CH=CH-
8-144	3,5-di-F-φ-	H,H	-CH₃	-φ	-CH₂-CH₂-
8-145	3,5-di-F-φ-	H,H	-CH₃	-φ	-N=CH-

TABLE 8-5



Ex.	R	X'/X''	R¹	R²
8-167	3,5-di-F-φ-	H.OH	-CH₃	-CH₃

TABLE 8C-1



$R^2 = 1$ position; $R^3 = 5$ position; $R^4 = 7$ position

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3,4-methylenedioxy-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2-CH ₃ O-φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-[(CH ₃) ₂ CH]φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
CH ₃ CH ₂ O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-(φ-O-)φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-CH ₃ CH ₂ O-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2,5-di-CH ₃ O-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2-CH ₃ -φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
(φ) ₂ CH-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
φ-O-CH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	R,S
indol-3-yl-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-CF ₃ -φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-CH ₃ -φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-HOCH ₂ -φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2-(φ-O-)φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3-(ϕ -O)- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	R,S
3,4-di-Cl- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	R,S
4-F- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	- ϕ	H	R,S
CH ₃ O-	H,H	-CH ₃	-CH ₃	- ϕ	H	R,S
ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-CH ₃ O- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-(<i>n</i> -C ₄ H ₉ O)- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CH ₃ O- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
(CH ₃) ₂ CH-O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
1- ϕ -tetrazol-5-yl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-(3,4-methylene- dioxy)- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
cyclopentyl-CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
cyclopenten-2-yl-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-F-6-Cl- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
cyclohexyl-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,5-di-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,3,4,5,6-penta-F- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3,5-di-CH ₃ - ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-Cl- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-Cl- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
benzo[b]thiophen-3-yl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -	=O	-CH ₃	-CH ₃	- ϕ	H	S
3,5-di-CH ₃ O- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,5-di-CH ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,6-di-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,4-di-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
mesityl	H,H	-CH ₃	-CH ₃	- ϕ	H	S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
ϕ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3,4-di-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
trans-styryl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -C(O)CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ CH=CH- (trans)	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ - ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-Cl- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH(ϕ)-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ O- ϕ -CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ OC(O)CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ CH ₂ SCH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ CH(CH ₃)-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CHCH ₂ CH ₂ CH ₂ - C(O)OCH ₃	H,H	-CH ₃	-CH ₃	- ϕ	H	S
indan-2-yl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ O- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-Cl- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-thienyl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,6-di-F- ϕ -	H,OH	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ O- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3,5-di-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-CH ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-Cl- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-naphthyl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-Cl- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-CH ₃ - ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3,4-methylenedioxy- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CH ₃ O- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-[(CH ₃) ₂ CH] ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4- ϕ -O- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -S-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ CH ₂ O- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,5-di-CH ₃ O- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CH ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
(ϕ) ₂ CH-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -O-CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
indol-3-yl-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3,5-di-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-(ϕ -O)- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-(ϕ -O)- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,4-di-Cl- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ S-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -	H,OH	-CH ₃	-CH ₃	- ϕ	H	S
4-thionaphthyl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-Cl- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
thien-2-yl-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3-CH ₃ O- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
(CH ₃) ₂ CHCH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ (CH ₂) ₅ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3-HO- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-HO- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
3,4,5-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
cyclopentyl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH- CF ₃	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CH ₃ -benzofuran-3-yl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
cyclopropyl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ OCH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
thienyl-CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -O-CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
norbornan-2-yl	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,3-di-F- ϕ -	H,OH	-CH ₃	-CH ₃	- ϕ	H	S
CH ₃ CH=CH-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,4-di-Cl- ϕ -O- CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,3-di-Cl- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-NO ₂ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-HOCH ₂ - ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-F-3-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2,4,6-tri-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F-2-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
CF ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-F-4-CF ₃ - ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-Br- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-F- ϕ -C(O)CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S
2-CH ₃ - ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
4-CH ₃ O- ϕ -O-	H,H	-CH ₃	-CH ₃	- ϕ	H	S
ϕ SO ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	H	S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
2-CH ₃ O-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
2-Br-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
4-[(CH ₃) ₂ CH]φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
CH ₂ =CHCH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	S
4-HO-φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	S
CH ₃ OCH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	S
2-HO-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
3,4-di-CH ₃ O-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
4-CH ₃ O-φ-C(O)CH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	S
thien-3-yl	H,H	-CH ₃	-CH ₃	-φ	H	S
φCH ₂ CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	S
(CH ₃) ₂ CH-	H,H	-CH ₃	-CH ₃	-φ	H	S
2,3,5-tri-F-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
2,4,5-tri-F-φ-	H,H	-CH ₃	-CH ₃	-φ	H	S
adamantan-1-yl	H,H	-CH ₃	-CH ₃	-φ	H	S
cyclohexyl- CH ₂ CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	-φ	H	S
thien-2-yl	H,H	-φ	-CH ₃	-φ	H	S
3-CF ₃ -φ-	H,H	-φ	-CH ₃	-φ	H	S
3,5-di-F-φ-	H,H	-φ	-CH ₃	-φ	H	S
3-CH ₃ -φ-	H,H	-φ	-CH ₃	-φ	H	S
3-F-φ-	H,H	-φ	-CH ₃	-φ	H	S
3-Br-φ-	H,H	-φ	-CH ₃	-φ	H	S
3-Cl-φ	H,H	-φ	-CH ₃	-φ	H	S
3,4-methylenedioxy-φ-	H,H	-φ	-CH ₃	-φ	H	S
φ-S-	H,H	-φ	-CH ₃	-φ	H	S
3,5-di-CF ₃ -φ-	H,H	-φ	-CH ₃	-φ	H	S
CH ₃ S-	H,H	-φ	-CH ₃	-φ	H	S
φ-O-	H,H	-φ	-CH ₃	-φ	H	S
φ-	H,H	-φ	-CH ₃	-φ	H	S
cyclohexyl	H,H	-φ	-CH ₃	-φ	H	S
2,5-di-F-φ-	H,H	-φ	-CH ₃	-φ	H	S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
benzo[b]thiophen-3-yl	H,H	-φ	-CH ₃	-φ	H	S
φ-	=O	-φ	-CH ₃	-φ	H	S
2,6-di-F-φ-	H,H	-φ	-CH ₃	-φ	H	S
2,4-di-F-φ-	H,H	-φ	-CH ₃	-φ	H	S
3,4-di-F-φ-	H,H	-φ	-CH ₃	-φ	H	S
CH ₃ CH ₂ -	H,H	-φ	-CH ₃	-φ	H	S
CH ₃ (CH ₂) ₄ -	H,H	-φ	-CH ₃	-φ	H	S
thien-2-yl-CH ₂ CH ₂ -	H,H	-φ	-CH ₃	-φ	H	S
(CH ₃) ₂ CHCH ₂ CH ₂ -	H,H	-φ	-CH ₃	-φ	H	S
φCH ₂ -	H,H	-φ	-CH ₃	-φ	H	S
cyclopentyl	H,H	-φ	-CH ₃	-φ	H	S
CH ₃ -	H,H	-φ	-CH ₃	-φ	H	S
3,4,5-CF ₃ -φ-	H,H	-φ	-CH ₃	-φ	H	S
φ-CH ₂ CH ₂ -	H,H	-φ	-CH ₃	-φ	H	S
2-thienyl	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S
2-thienyl	H,H	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	-φ	Cl	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	2-Cl-φ	Cl	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
2-thienyl	H,H	-CH ₃	-CH ₃	-2-F-φ	Br	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	-φ	Cl	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	2-Cl-φ-	Cl	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	thien-2-yl	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	-cyclohexyl	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	2-F-φ-	Br	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3-F- ϕ -	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	thien-2-yl	H	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
3-F- ϕ -	H,H	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
CH ₃ S-	H,H	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
ϕ -	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
ϕ -	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
ϕ -	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
ϕ -	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
ϕ -	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
ϕ -	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
ϕ -	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
ϕ -	=O	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
ϕ -	=O	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
ϕ -	=O	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
ϕ -	=O	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
ϕ -	=O	-CH ₃	-CH ₃	2-thienyl	H	R,S
ϕ -	=O	-CH ₃	-CH ₃	cyclohexyl	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
ϕ -	=O	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
(2-thienyl)-CH ₂ CH ₂ -	H,H	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
cyclopentyl	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	- ϕ	Cl	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	2-Cl- ϕ -	Cl	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₃	2-F- ϕ -	Br	R,S
CH ₃ CH- CF ₃	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	- ϕ	H	R,S
CH ₃ CH- CF ₃	H,H	-CH ₃	-CH ₂ C(O) ϕ	- ϕ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	-φ	Cl	R,S
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	2-Cl-φ	Cl	R,S
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
$\text{CH}_3\text{CH}-$ CF_3	H,H	-CH ₃	-CH ₃	2-F-φ-	Br	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	-φ	Cl	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	2-Cl-φ-	Cl	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
CF_3CH_2-	H,H	-CH ₃	-CH ₃	2-F-φ-	Br	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	-φ	Cl	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	2-Cl-φ-	Cl	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	2-thienyl	H	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	cyclohexyl	H	R,S
$(\text{CH}_3)_2\text{CH}-$	H,H	-CH ₃	-CH ₃	2-F-φ-	Br	R,S
$(\text{CH}_3)_2\text{CHCH}_2-$	H,OH	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	-φ	Cl	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	2-Cl-φ-	Cl	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	2-thienyl	H	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	cyclohexyl	H	R,S
(CH ₃) ₂ CHCH ₂ -	H.OH	-CH ₃	-CH ₃	2-F-φ-	Br	R,S
-φ	H.OH	-CH ₃	-CH ₂ CH ₂ - CH ₂ CF ₃	-φ	H	R,S
-φ	H.OH	-CH ₃	-CH ₂ C(O)φ	-φ	H	R,S
-φ	H.OH	-CH ₃	-CH ₃	2-thiazolyl	H	R,S
-φ	H.OH	-CH ₃	-CH ₃	-φ	Cl	R,S
-φ	H.OH	-CH ₃	-CH ₃	2-Cl-φ-	Cl	R,S
-φ	H.OH	-CH ₃	-CH ₃	2-thienyl	H	R,S
-φ	H.OH	-CH ₃	-CH ₃	cyclohexyl	H	R,S
-φ	H.OH	-CH ₃	-CH ₃	2-F-φ-	Br	R,S
3,5-di-F-φ-	H,H	-CH ₃	3-F-φ-	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₂ φ	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	4- <i>t</i> -butyl- CH ₂ φ	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₂ CH ₂ - cyclohexyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3,3-dimethyl- butyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	CH ₃ OC(O)- CH(φ)-	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-ethyl- butyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	cyclohexyl- methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-φ-ethyl-	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3-φ-propyl-	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-(N- phthalimidyl) ethyl	-φ	H	R,S

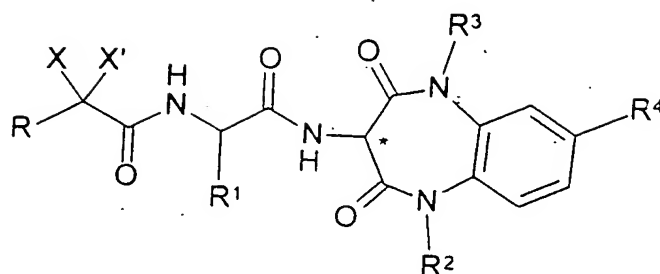
R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
3,5-di-F-φ-	H,H	-CH ₃	2-biphenyl- methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-tetrahydro- furan-yl- methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-(1,4-benzo- dioxanyl) methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3-(5-chloro- benzo[b]thien- -yl)methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3,3-dimethyl- 2-oxo-propyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	5-benzofuraz- anylmethyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3-(φ-O)- propyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	6-(2-CF ₃ - quinoliny) methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-methylbutyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	ethyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	3-pyridyl- methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-oxo-2-(N- indoliny)- ethyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	4-(3,5-di- methyl- isoxazolyl) methyl	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2-CH ₃ O-ethyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₂ φ	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	(4- <i>r</i> -butyl-) CH ₂ φ	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	-CH ₂ CH ₂ - cyclohexyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	3,3-dimethyl- butyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	isopropyl	-φ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
cyclopentyl	H,H	-CH ₃	CH ₃ OC(O)- CH(φ)-	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-ethyl- butyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	cyclohexyl- methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-φ-ethyl-	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	3-φ-propyl-	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-(N- phthalimidyl) ethyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-biphenyl- methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	3-(5-chloro- benzo[b]thien- -yl)methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	3,3-dimethyl- 2-oxo-butyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	5-benzofuraz- anylmethyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	3-(φ-O)- propyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	6-(2-CF ₃ - quinoliny)l methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	cyclopropyl- methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-methyl- butyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	ethyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	4-(3,5-di- methyl- isoxazoly)l methyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	propyl	-φ	H	R,S
cyclopentyl	H,H	-CH ₃	2-CH ₃ O-ethyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	-CH ₂ φ	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	(4-(t-butyl)- CH ₂ φ	-φ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
CF ₃ CH ₂ -	H,H	-CH ₃	-CH ₂ CH ₂ - cyclohexyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	3,3-dimethyl- butyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	isopropyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	CH ₃ OC(O)- CH(φ)-	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	2-ethyl- butyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	cyclohexyl- methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	3-φ-propyl-	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	2-biphenyl- methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	3-(5-chloro- benzo[b]thien- -yl)methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	3,3-dimethyl- 2-oxo-butyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	5-benzofuraz- anylmethyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	3-(φ-O)- propyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	6-(2-CF ₃ - quinolinyl) methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	cyclopropyl- methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	2-methyl- butyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	ethyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	4-(3,5-di- methyl- isoxazolyl) methyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	propyl	-φ	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	2-CH ₃ O-ethyl	-φ	H	R,S
N-pyrrolidinyl	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2-Cl-φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S

R	X and X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
2-thienyl	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3-CF ₃ -φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-CH ₃ -φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-CH ₃ O-φ-CH ₃ -	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3-CH ₃ -φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3-F-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3-Br-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
4-Cl-O-φ-	H,H	-CH ₃	-CH ₃	-φ	H	R,S
2-naphthyl	H,H	-CH ₃	-CH ₃	-φ	H	R,S
3-CH ₃ -φ-O-	H,H	-CH ₃	-CH ₃	-φ	H	R,S

TABLE 8C-2



$R^2 = 1$ position; $R^3 = 5$ position; $R^4 = 7$ position

R	X/X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
2-thienyl	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
3,5-di-F-φ-	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
3-F-φ-	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
CH ₃ S-	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
φ-	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
φ-	=O	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
CH ₃ CH ₂ -	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
2-thienyl-CH ₃ CH ₂ -	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
cyclopentyl	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
CH ₃ CH- CF ₃	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
CF ₃ CH ₂ -	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S
(CH ₃) ₂ CH-	H,H	-CH ₃	2,2-di-CH ₃ -propyl	2,2-di-CH ₃ -propyl	H	R,S

R	X/X'	R ¹	R ²	R ³	R ⁴	Iso. (at *)
(CH ₃) ₂ CHCH ₂ -	OH.H	-CH ₃	2,2-di-CH ₃ - propyl	2,2-di- CH ₃ -propyl	H	R,S
φ-	OH.H	-CH ₃	2,2-di-CH ₃ - propyl	2,2-di- CH ₃ -propyl	H	R,S

Also included within the scope of this invention are prodrugs of the compounds of formula I above including acylated forms of alcohols and thiols, amination of one or more amines, and the like.

5 **DETAILED DESCRIPTION OF THE INVENTION**

As above, this invention relates to compounds which inhibit β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. However, prior to describing this invention in further detail, the following terms will first be defined.

10

Definitions

The term " β -amyloid peptide" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kD, which peptide is substantially homologous to the form of the protein described by Glenner, et al.¹ including mutations and post-translational modifications of the normal β -amyloid peptide. In whatever form, the β -amyloid peptide is an approximate 39-43 amino acid fragment of a large membrane-spanning glycoprotein, referred to as the β -amyloid precursor protein (APP). Its 43-amino acid sequence is:

20

1
Asp Ala Glu Phe Arg His Asp Ser Gly Tyr

25

11
Glu Val His His Gln Lys Leu Val Phe Phe

21
Ala Glu Asp Val Gly Ser Asn Lys Gly Ala

30

31
Ile Ile Gly Leu Met Val Gly Gly Val Val

35

41
Ile Ala Thr (SEQ ID NO: 1)

or a sequence which is substantially homologous thereto.

"Alkyl" refers to monovalent alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

5

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

10

15

20

"Alkylene" refers to divalent alkylene groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

25

"Substituted alkylene" refers to an alkylene group, preferably of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono-

30

and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

Additionally, such substituted alkylene groups include those where 2

5 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused cycloalkyl groups contain from 1 to 3 fused ring structures.

"Alkenylene" refers to divalent alkenylene groups preferably having
10 from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms. This term is exemplified by groups such as ethenylene ($-\text{CH}=\text{CH}-$), the propenylene isomers (e.g., $-\text{CH}_2\text{CH}=\text{CH}-$ and $-\text{C}(\text{CH}_3)=\text{CH}-$) and the like.

"Substituted alkenylene" refers to an alkenylene group, preferably of
15 from 2 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, and mono- and di-alkylamino, mono- and di-(substituted
20 alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic. Additionally, such substituted alkylene groups include those
25 where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group.

"Alkaryl" refers to -alkylene-aryl groups preferably having from 1 to 8 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

"Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

5

"Substituted alkoxy" refers to the group "substituted alkyl-O-" where substituted alkyl is as defined above.

10 "Alkylalkoxy" refers to the group "-alkylene-O-alkyl" which includes by way of example, methylenemethoxy ($-\text{CH}_2\text{OCH}_3$), ethylenemethoxy ($-\text{CH}_2\text{CH}_2\text{OCH}_3$), *n*-propylene-*iso*-propoxy ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)_2$), methylene-*t*-butoxy ($-\text{CH}_2-\text{O}-\text{C}(\text{CH}_3)_3$) and the like.

15 "Alkylthioalkoxy" refers to the group "-alkylene-S-alkyl" which includes by way of example, methylenethiomethoxy ($-\text{CH}_2\text{SCH}_3$), ethylenethiomethoxy ($-\text{CH}_2\text{CH}_2\text{SCH}_3$), *n*-propylene-thio-*iso*-propoxy ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{SCH}(\text{CH}_3)_2$), methylenethio-*t*-butoxy ($-\text{CH}_2\text{SC}(\text{CH}_3)_3$) and the like.

20 "Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl ($-\text{CH}=\text{CH}_2$), *n*-propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), *iso*-propenyl ($-\text{C}(\text{CH}_3)=\text{CH}_2$), and the like.

25 "Substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, -SO-alkyl, -SO-substituted alkyl, 30 -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl,

5 -SO₂-heteroaryl, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

10 "Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation. Preferred alkynyl groups include ethynyl (-CH≡CH₂), propargyl (-CH₂C≡CH) and the like.

15 "Substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

25 "Acyl" refers to the groups alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

30 "Acylamino" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic

wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Aminoacyl" refers to the group -NRC(O)R where each R is
5 independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Aminoacyloxy" refers to the group -NRC(O)OR where each R is
10 independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O- , $\text{substituted alkyl-C(O)O-}$,
15 cycloalkyl-C(O)O- , aryl-C(O)O- , heteroaryl-C(O)O- , and $\text{heterocyclic-C(O)O-}$ wherein alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to
20 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

Unless otherwise constrained by the definition for the aryl substituent,
25 such aryl groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of acyloxy, 1 to 5 and preferably 1 to 3 substituents selected from the group consisting of hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido,
30 carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heterocyclic,

aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl, trihalomethyl, mono- and di-alkylamino, mono- and di-
5 (substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic, and the like. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

10

"Aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

15 "Carboxyalkyl" refers to the group "-C(O)Oalkyl" where alkyl is as defined above.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl,
20 cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

"Substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 (preferably 1 to 3) substituents selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl,
25 substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like.

30 "Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 8 carbon atoms having a single cyclic ring and at least one point of internal unsaturation.

Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

5 "Substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like.

10 "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either fluoro or chloro.

"Heteroaryl" refers to an aromatic carbocyclic group of from 1 to 15
15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl
substituent, such heteroaryl groups can be optionally substituted with 1 to 5
20 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, halo, nitro, heteroaryl, thiol, thioalkoxy, substituted thioalkoxy, thioaryloxy, trihalomethyl and the like. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include
25 pyridyl, pyrrolyl and furyl.

"Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 15
carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or
30 oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, halo, nitro, heteroaryl, thiol, thioalkoxy, substituted thioalkoxy, thioaryloxy, trihalomethyl, and the like. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

"Oxyacylamino" refers to the group $-OC(O)NRR$ where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Thiol" refers to the group $-SH$.

"Thioalkoxy" refers to the group $-S-alkyl$.

"Substituted thioalkoxy" refers to the group $-S-substituted alkyl$.

"Thioaryloxy" refers to the group $aryl-S-$ wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

"Thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

5 As to any of the above groups which contain 1 or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

10 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic
15 functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like can be used as the pharmaceutically acceptable salt.

20 The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, amino or carboxyl groups of the compounds (including intermediates thereof such as the aminolactams, aminolactones, etc.) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, amino or carboxyl group. The particular removable
25 blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzyldine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild
30 conditions compatible with the nature of the product.

Preferred removable amino blocking groups include conventional substituents such as t-butyloxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

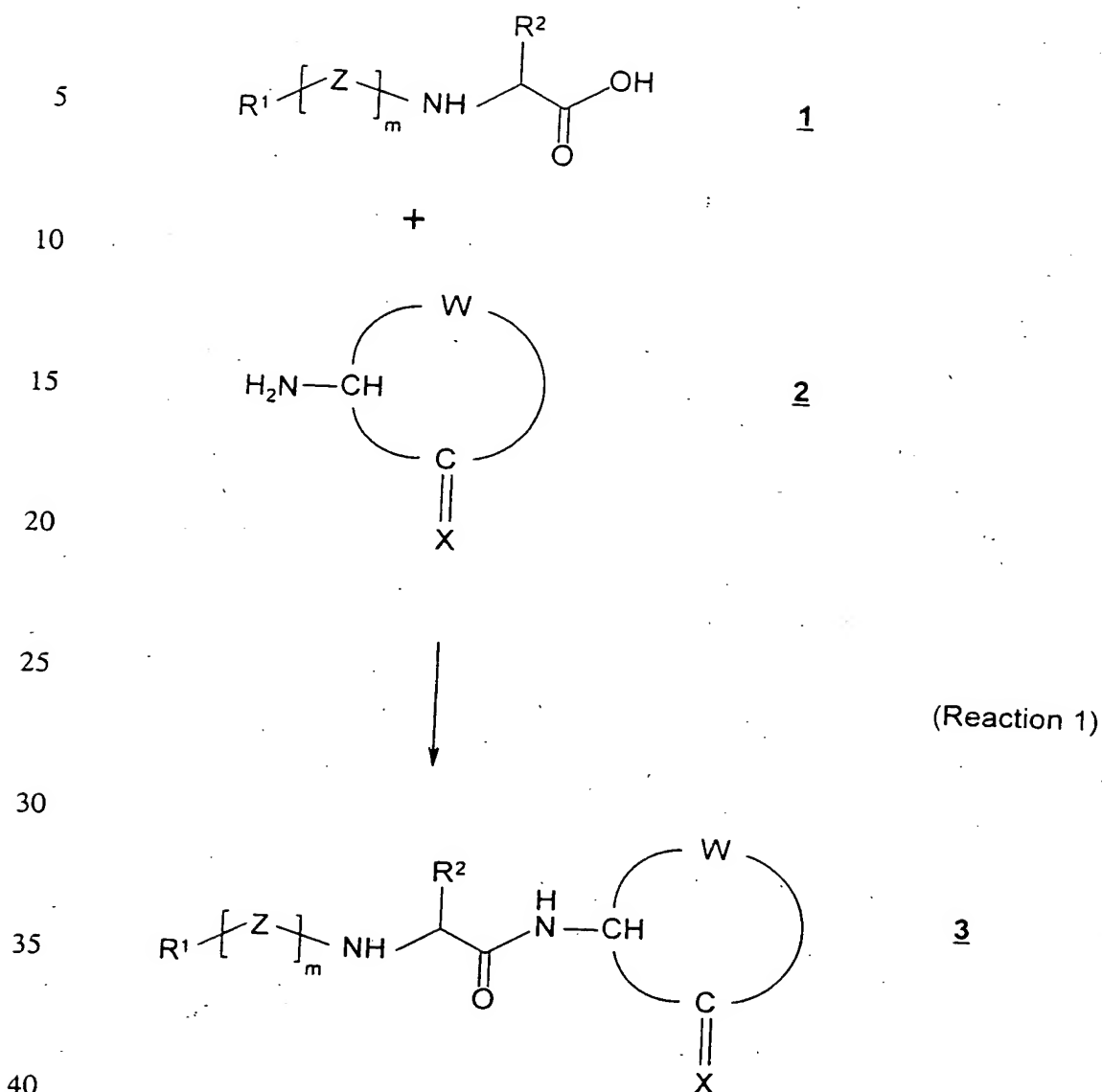
5

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

10

Compound Preparation

When n is one or two, the compounds of formula I are readily prepared by conventional amidation of a carboxyl acid as shown in reaction (1) below where, for the sake of illustration, n is one:



wherein R^1 , R^2 , W , X , Z and m are as defined above. The reaction is conventionally conducted by using at least a stoichiometric amount of carboxylic acid 1 and amine 2. This reaction is conventionally conducted for peptide synthesis and synthetic methods used therein can also be employed to prepare compound 3 which is a compound of formula I above. For example, well known coupling reagents such as carbodiimides with or without the use of well known additives such as N-hydroxysuccinimide, 1-hydroxybenzotriazole,

etc. can be used to facilitate coupling. The reaction is conventionally conducted in an inert aprotic polar diluent such as dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like. Alternatively, the acid halide of compound 1 can be employed in reaction (1) and, when so employed, it is typically employed in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, N-methylmorpholine and the like.

When n is zero, the compounds of formula I can be prepared by N-substitution reactions of compound 2. For example, when $m = 0$ and $n = 0$, N-arylation reactions on compound 2 lead to compounds of formula I. When $m = 1$ and $n = 0$, reaction of compound 2 with an acetic acid derivative represented by the formula R^1-T-CH_2-COOH also lead to compounds of formula I. Both reactions are described below.

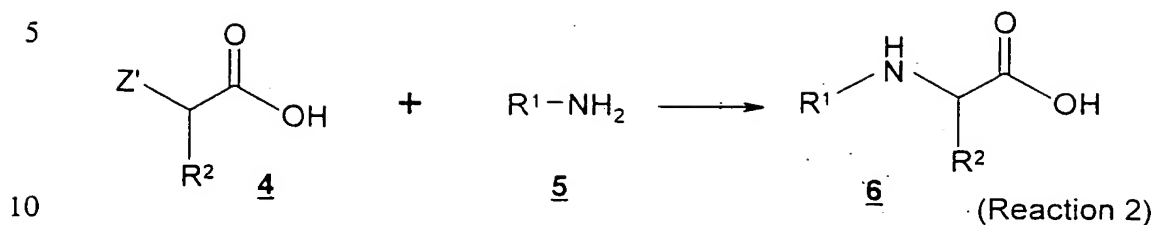
Synthesis of Carboxylic Acid Starting materials

Carboxylic acids 1 can be prepared by several divergent synthetic routes with the particular route selected relative to the ease of compound preparation, commercial availability of starting materials, whether m is zero or one, whether n is one or two, etc.

A. Synthesis of Carboxylic Acids

When m is zero and n is one, a first synthetic method involves the introduction of the R^1 group to the amino acid $NH_2CH(R^2)COOH$ or ester thereof.

The introduction of the R^1 group onto the amino acid $NH_2CH(R^2)COOH$ or ester thereof can be accomplished in several methods. For example, conventional coupling of a halo acetic acid with a primary amine forms an amino acid as shown in reaction (2) below:



15 wherein R^1 and R^2 are as defined above and Z' is a halo group such as chloro or bromo. Alternatively, leaving groups other than halo may be employed such as triflate and the like. Additionally, suitable esters of 4 may be employed in this reaction.

20 As above, reaction (2) involves coupling of a suitable haloacetic acid derivative 4 with a primary amine 5 under conditions which provide for amino acid 6. This reaction is described by, for example, Yates, et al.¹⁴ and proceeds by combining approximately stoichiometric equivalents of haloacetic acid 4 with primary amine 5 in a suitable inert diluent such as water, dimethylsulfoxide (DMSO) and the like. The reaction employs an excess of a suitable base such as sodium bicarbonate, sodium hydroxide, etc. to scavenge the acid generated by the reaction. The reaction is preferably conducted at from about 25°C to about 100°C until reaction completion which typically occurs within 1 to about 24 hours. This reaction is further described in U.S. Patent No. 3,598,859, which is incorporated herein by reference in its entirety. Upon reaction completion, N-substituted amino acid 6 is recovered by conventional methods including precipitation, chromatography, filtration and the like.

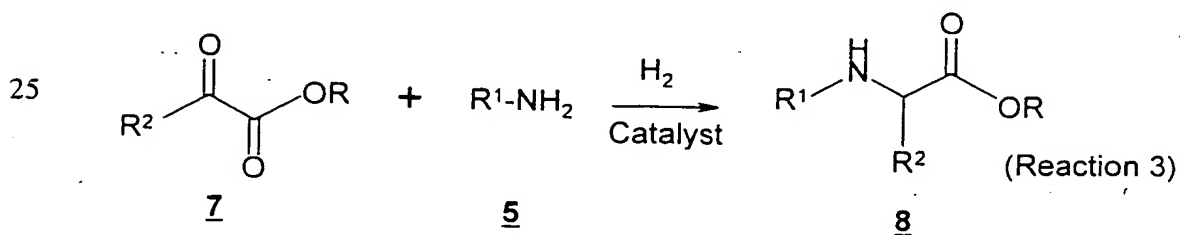
25

30

In reaction (2), each of the reagents (haloacetic acid 4, primary amine 5 and alcohol 6) are well known in the art with a plurality of each being commercially available.

5 In an alternative embodiment, the R¹ group can be coupled to an alanine ester (or other suitable amino acid ester) by conventional N-arylation. For example, a stoichiometric equivalent or slight excess of the amino acid ester can be dissolved in a suitable diluent such as DMSO and coupled with a halo-R¹ compound, Z'-R¹ where Z' is a halo group such as chloro or bromo and R¹ is
10 as defined above. The reaction is conducted in the presence of an excess of base such as sodium hydroxide to scavenge the acid generated by the reaction. The reaction typically proceeds at from 15°C to about 250°C and is complete in about 1 to 24 hours. Upon reaction completion, N-substituted amino acid ester is recovered by conventional methods including chromatography, filtration
15 and the like. This ester is then hydrolyzed by conventional methods to provide for carboxylic acid 1 for use in reaction (1).

In still another alternative embodiment, the esterified amino acids of formula I above can be prepared by reductive amination of a suitable pyruvate ester in the manner illustrated in reaction (3) below:
20



wherein R is typically an alkyl group and R¹ and R² are as defined above.

5 In reaction (3), approximately stoichiometric equivalents of pyruvate ester 7 and amine 5 are combined in an inert diluent such as methanol, ethanol and the like and the reaction solution treated under conditions which provide for imine formation (not shown). The imine formed is then reduced under conventional conditions by a suitable reducing agent such as sodium cyanoborohydride, H₂/palladium on carbon and the like to form the /N-substituted amino acid ester 8. In a particularly preferred embodiment, the 10 reducing agent is H₂/palladium on carbon which is incorporated into the initial reaction medium which permits imine reduction *in situ* in a one pot procedure to provide for the N-substituted amino acid ester 8.

15 The reaction is preferably conducted at from about 20°C to about 80°C at a pressure of from 1 to 10 atmospheres until reaction completion which typically occurs within 1 to about 24 hours. Upon reaction completion, N-substituted amino acid ester 8 is recovered by conventional methods including chromatography, filtration and the like.

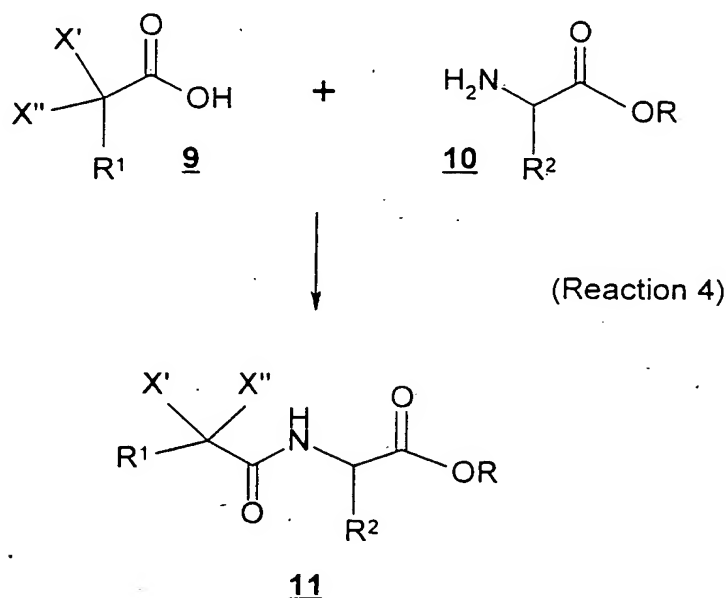
20 Subsequent hydrolysis of the ester 8 leads to the corresponding carboxylic acid derivative 1 which can be employed in reaction (1) above.

25 For compounds where *m* is zero and *n* is two, conventional coupling of a second amino acid (e.g., NH₂CH(R²)C(O)OR where R is typically an alkyl group) to the amino acid produced above (i.e., R¹NHCH(R²)COOH) provides for esters of an analogue of carboxylic acid 1 which are then conventionally de-esterified to provide for an analogue of compound 1.

30 Alternatively, an ester such as H₂NCH(R²)C(O)NHCH(R²)COOR where each R² is independently as defined above and R is typically an alkyl group can first be formed by conventional peptide synthetic procedures, N-substitution can

be conducted in the manner described above followed by de-esterification to provide for analogues of carboxylic acids 1 where n is two.

When m is one and n is one, a first synthetic method involves
5 conventional coupling of an acetic acid derivative with a primary amine of an esterified amino acid as shown in reaction (4) below:



wherein R is typically an alkyl group and R¹, R², X' and X'' are as defined above.

35 Reaction (4) merely involves coupling of a suitable acetic acid derivative 9 with the primary amine of amino acid ester 10 under conditions which provide for the N-acetyl derivative 11. This reaction is conventionally conducted for peptide synthesis and synthetic methods used therein can also be
40 employed to prepare the N-acetyl amino acid esters 11 of this invention. For

example, well known coupling reagents such as carbodiimides with or without the use of well known additives such as N-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. can be used to facilitate coupling. The reaction is conventionally conducted in an inert aprotic polar diluent such as

5 dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like. Alternatively, the acid halide of compound 9 can be employed in reaction (4) and, when so employed, it is typically employed in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, N-

10 methylmorpholine and the like.

Reaction (4) is preferably conducted at from about 0°C to about 60°C until reaction completion which typically occurs within 1 to about 24 hours. Upon reaction completion, N-acetyl amino acid ester 11 is recovered by

15 conventional methods including precipitation, chromatography, filtration and the like or alternatively is hydrolyzed to the corresponding acid without purification and/or isolation other than conventional work-up (e.g., aqueous extraction, etc.).

20 In reaction (4), each of the reagents (acetic acid derivative 9 and amino acid ester 10) are well known in the art with a plurality of each being commercially available.

When *m* is one and *n* is two, a further amino acid ester is coupled to the

25 amino acid ester 11 by first de-esterifying 11 and then using well known peptide coupling chemistry with well known coupling reagents such as carbodiimides with or without the use of well known additives such as N-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. which can be used to facilitate coupling. The reaction is conventionally conducted in an inert aprotic

30 polar diluent such as dimethylformamide, dichloromethane, chloroform,

acetonitrile, tetrahydrofuran and the like. De-esterification of the resulting ester provides for carboxylic acids 1 having n equal to 2.

Alternatively, carboxylic acids 1 having n equal to 2 can be prepared by
5 first forming the ester, N-acetylating these esters and then de-esterifying the resulting product.

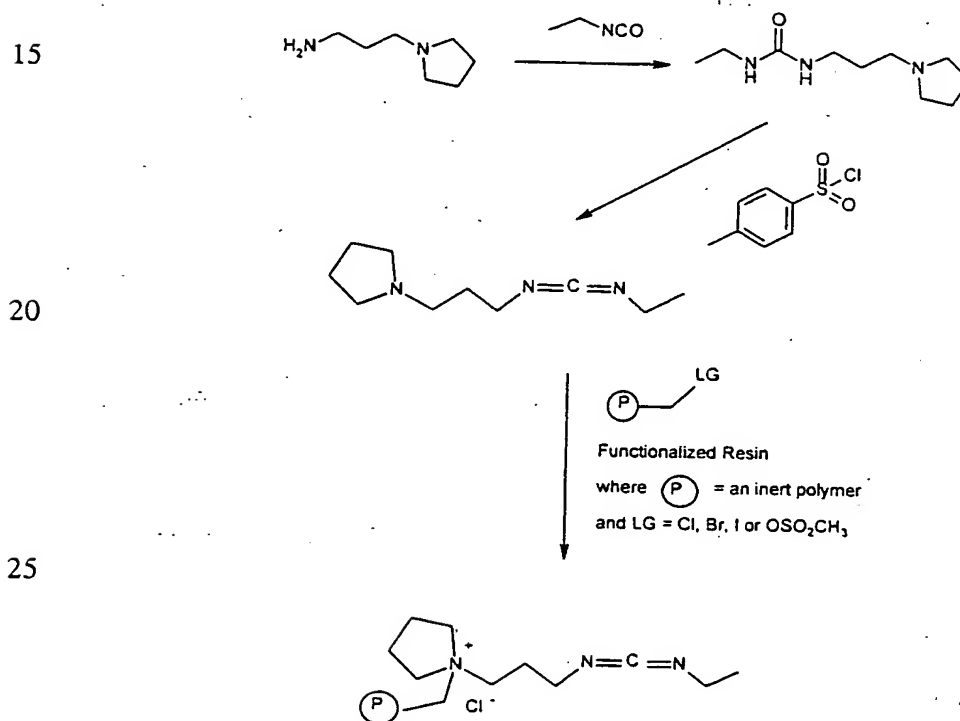
Carboxylic acids 1 having m equal to 1 and n equal to 1 or 2 can also be prepared by use of polymer supported forms of carbodiimide peptide coupling
10 reagents. A polymer supported form of EDC, for example, has been described (*Tetrahedron Letters*, 34(48), 7685 (1993))¹⁰. Additionally, a new carbodiimide coupling reagent, PEPC, and its corresponding polymer supported forms have been discovered and are very useful for the preparation of such compounds.

15 Polymers suitable for use in making a polymer supported coupling reagent are either commercially available or may be prepared by methods well known to the artisan skilled in the polymer arts. A suitable polymer must possess pendant sidechains bearing moieties reactive with the terminal amine of the carbodiimide. Such reactive moieties include chloro, bromo, iodo and
20 methanesulfonyl. Preferably, the reactive moiety is a chloromethyl group. Additionally, the polymer's backbone must be inert to both the carbodiimide and reaction conditions under which the ultimate polymer bound coupling reagents will be used.

25 Certain hydroxymethylated resins may be converted into chloromethylated resins useful for the preparation of polymer supported coupling reagents. Examples of these hydroxylated resins include the 4-hydroxymethylphenylacetamidomethyl resin (Pam Resin) and 4-benzyloxybenzyl alcohol resin (Wang Resin) available from Advanced
30 Chemtech of Louisville, Kentucky, USA (see Advanced Chemtech 1993-1994 catalog, page 115). The hydroxymethyl groups of these resins may be

converted into the desired chloromethyl groups by any of a number of methods well known to the skilled artisan.

Preferred resins are the chloromethylated styrene/divinylbenzene resins because of their ready commercial availability. As the name suggests, these resins are already chloromethylated and require no chemical modification prior to use. These resins are commercially known as Merrifield's resins and are available from Aldrich Chemical Company of Milwaukee, Wisconsin, USA (see Aldrich 1994-1995 catalog, page 899). Methods for the preparation of PEPC and its polymer supported forms are outlined in the following scheme.

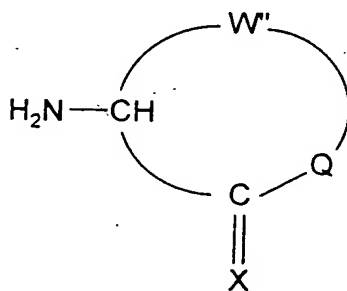


Such methods are described more fully in U.S. Patent Application Serial No. 60/019,790 filed June 14, 1996 which application is incorporated herein by reference in its entirety. Briefly, PEPC is prepared by first reacting ethyl isocyanate with 1-(3-aminopropyl)pyrrolidine. The resulting urea is treated
5 with 4-toluenesulfonyl chloride to provide PEPC. The polymer supported form is prepared by reaction of PEPC with an appropriate resin under standard conditions to give the desired reagent.

The carboxylic acid coupling reactions employing these reagents are
10 performed at about ambient to about 45°C, for from about 3 to 120 hours. Typically, the product may be isolated by washing the reaction with CHCl₃ and concentrating the remaining organics under reduced pressure. As discussed *supra*, isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture
15 and then concentration of the filtrate under reduced pressure.

Preparation of Cyclic Amino Compounds

Cyclic amino compounds 2 employed in reaction (1) above are generally aminolactams, aminolactones, aminothiolactones and aminocycloalkyl
20 compounds which can be represented by the formula:

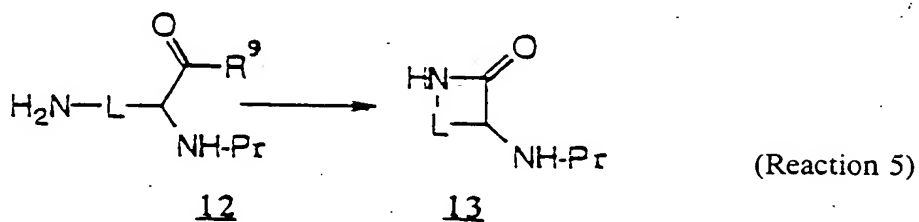


where X is as defined above, Q is preferably selected from the group consisting of -O-, -S-, >NR⁶, and >CR⁷R⁸ where each of R⁶, R⁷ and R⁸ are
35 independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl

and heterocyclic with the proviso that if Q is -O-, -S- or >NR⁶, then X is oxo or dihydro, and W" together with Q, C=X and CH forms a lactone, thiolactone, lactam, cyclic ketone, cyclic alcohol, a heterocycle, and the like.

5 The aminolactams, aminolactones and aminothirolactones of the formula above can be prepared by use or adaptation of known chemical syntheses which syntheses are well described in the literature. See, e.g., Ogliaruso and Wolfe, *Synthesis of Lactones and Lactams*, Patai, et al. Editor, J. Wiley & Sons, New York, New York, USA, pp. 1085 et seq. (1993)¹⁵.

10 Specifically, 3-amino substituted lactams 13 with 5, 6 or 7 ring atoms may be prepared by the direct cyclization of a suitable alpha, omega-diamino acid ester 12 as shown in reaction (5) below:

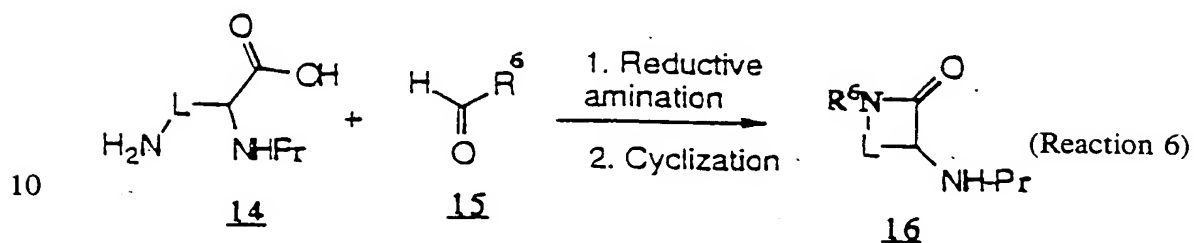


20 wherein L is a linking group (typically an alkylene group) of from 2-4 atoms, Pr is a suitable protecting group such as *t*-butoxycarbonyl, carbobenzyloxy, or the like and R⁹ is an alkoxy or aryloxy group such as methoxy, ethoxy, *p*-nitrophenoxy, *N*-succinimidoxo, and the like. The reaction may be carried
25 out in a solvent such as water, methanol, ethanol, pyridine, and the like. Such reactions are exemplified by cyclization of a lysine ester to a caprolactam as described by Ugi, et al., *Tetrahedron*, 52(35):11657-11664 (1996)¹⁶.

30 Alternatively, such a cyclization can also be conducted in the presence of dehydrating agents such as alumina or silica to form lactams as described by Blade-Font, *Tetrahedron Lett.*, 21:2443 (1980)¹⁷.

The preparation of aminolactams alkylated on the amino group of the cyclic lactam is described by Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982)¹⁸ and illustrated in reaction (6) below:

5

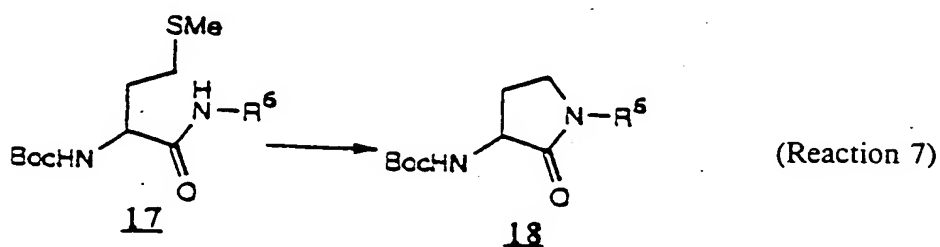


wherein L and R⁶ are as defined above.

15 In reaction (6), reductive amination of 14 with aldehyde 15 and subsequent ring closure by methods using, for example, EDC provides for aminolactam 16. The preparation of 6 membered lactams using this general procedure is described by Semple, et al., *J. Med. Chem.*, 39:4531-4536 (1996)¹⁹.

20 The internal cyclization of an amide anion with a halide or equivalent thereof can sometimes be used to particular advantage in the synthesis of smaller ring lactams where the stereochemistry of the amino-lactam center is available from the standard amino-acid pool. This approach is illustrated in reaction (7) below:

25

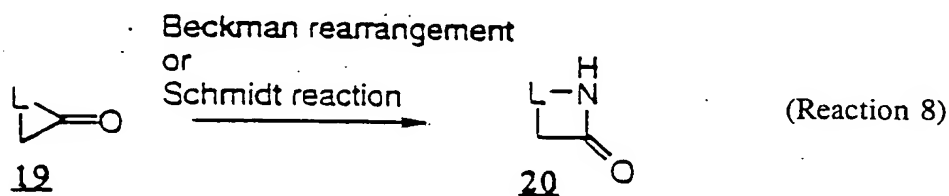


30

where R⁶ is as defined above.

The approach of reaction (7) is presented by Semple, et al., *supra*.¹⁹, and Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982)¹⁸ where a dimethylsulfonium leaving group is generated from methyl iodide treatment of an alkyl methyl sulfide 17 to provide for lactam 18. A similar approach using a Mitsunobu reaction on an omega alcohol is found Holladay, et al., *J. Org. Chem.*, 56:3900-3905 (1991)²⁰.

In another method, lactams 20 can be prepared from cyclic ketones 19 using either the well known Beckmann rearrangement (e.g., Donaruma, et al., *Organic Reactions*, 11:1-156 (1960))²¹ or the well known Schmidt reaction (Wolff, *Organic Reactions*, 3:307-336 (1946))²² as shown in reaction (8) below:



20 wherein L is as defined above.

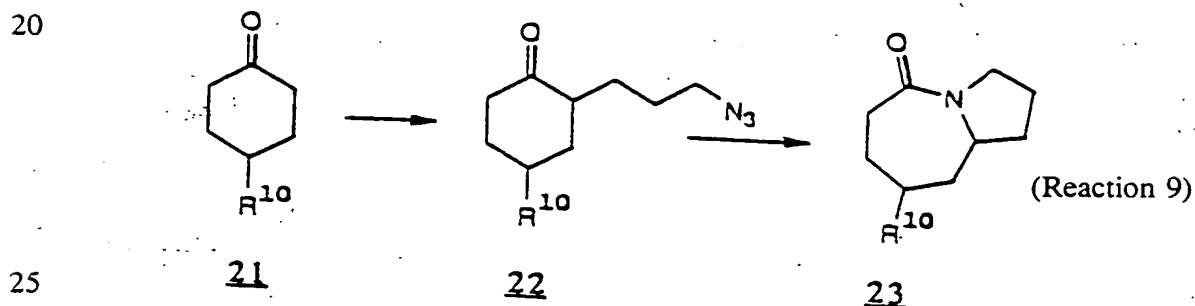
Application of these two reactions leads to a wide variety of lactams especially lactams having two hydrogen atoms on the carbon alpha to the lactam carbonyl which lactams form a preferred group of lactams in the synthesis of the compounds of formula I above. In these reactions, the L group can be highly variable including, for example, alkylene, substituted alkylene and hetero containing alkylene with the proviso that a heteroatom is not adjacent to the carbonyl group of compound 19. Additionally, the Beckmann rearrangement

25
30

can be applied to bicyclic ketones as described in Krow, et al., *J. Org. Chem.*, 61:5574-5580 (1996)²³.

The preparation of lactones can be similarly conducted using peracids in a Baeyer-Villiger reaction on ketones. Alternatively, thiolactones can be prepared by cyclization of an omega -SH group to a carboxylic acid and thiolactams can be prepared by conversion of the oxo group to the thiooxo group by P_2S_5 or by use of the commercially available Lawesson's Reagent, *Tetrahedron*, 35:2433 (1979)²⁴.

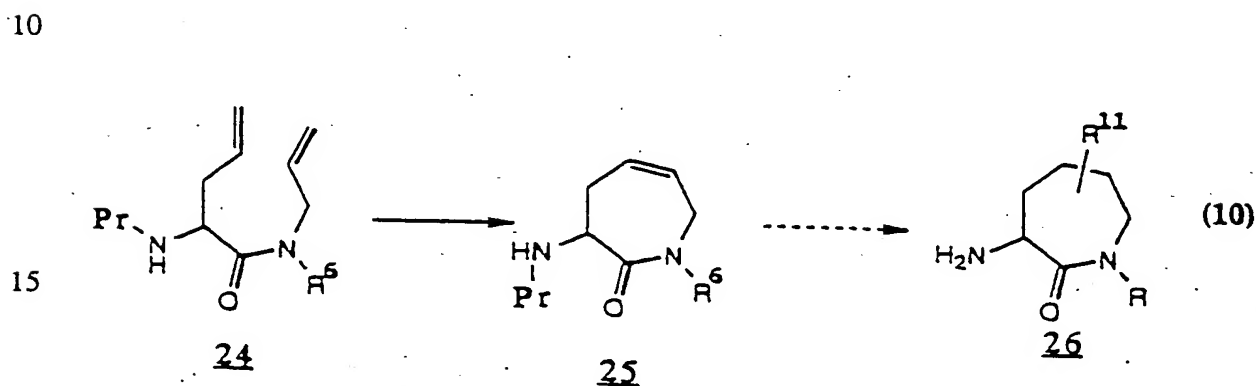
One recently reported route for lactam synthesis is a variation of the Schmidt reaction through the use of an alkyl azide, either intermolecularly or intramolecularly, through a tethered alkylazide function that attacks a ketone under acidic conditions. Gracias, et al., *J. Am. Chem. Soc.*, 117:8047-8048 (1995)²⁵ describes the intermolecular version whereas Milligan, et al., *J. Am. Chem. Soc.*, 117:10449-10459 (1995)²⁶ describes the intramolecular version. One example of the intramolecular version is illustrated in reaction (9) below:



where R^{10} is exemplified by alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, heteroaryl, cycloalkyl and heterocyclic.

In this reaction, ketone 21 is converted to an α -(ω -alkyl)ketone 22 which is cyclized to form bicyclic lactam 23. Such intramolecular reactions are useful in forming bicyclic lactams having 5-7 members and the lactam ring of 6-13 members. The use of hetero atoms at non-reactive sites in these rings is feasible in preparing heterobicyclic lactams.

Still another recent approach to the synthesis of lactams is described by Miller, et al., *J. Am. Chem. Soc.*, 118:9606-9614 (1996)²⁷ and references cited and is illustrated in reaction (10) below:



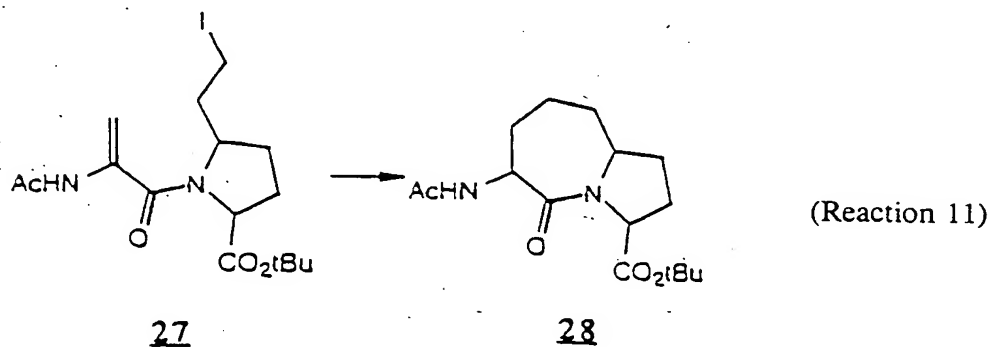
where R^6 and Pr are as defined above and R^{11} is exemplified by halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, heteroaryl, cycloalkyl and heterocyclic wherein the aryl, heteroaryl, cycloalkyl and heterocyclic group is optionally fused to the lactam ring structure.

Specifically, in reaction (10), lactam 26 is formed from an appropriate unsaturated amide (e.g., 24) through a ruthenium or molybdenum complexes catalyzed olefin metathesis reaction to form unsaturated lactam 25 which can be used herein without further modification. However, the unsaturation in 25 permits a myriad of techniques such as hydroboration, Sharpless or Jacobsen epoxidations, Sharpless dihydroxylations, Diels-Alder additions, dipolar cycloaddition reactions and many more chemistries to provide for a wide range

of substituents on the lactam ring. Moreover, subsequent transformations of the formed substitution leads to other additional substituents (e.g., mesylation of an alcohol followed by nucleophilic substitution reactions). See, for example, March, et al. for a recitation of numerous such possible reactions.²⁸

Saturated amides used in this reaction are conventional with amide 24 being commercially available.

Related chemistry to cyclize amides to form lactams is disclosed by Colombo, et al., *Tetrahedron Lett.*, 35(23):4031-4034 (1994)²⁹ and is illustrated in reaction (11) below:



In this reaction, proline derivative 27 is cyclized via a tributyltin-radical cyclization to provide for lactam 28.

Some of the lactams described above contain the requisite amino group alpha to the lactam carbonyl whereas others did not. However, the introduction of the required amino group can be achieved by any of several routes delineated below which merely catalogue several recent literature references for this synthesis.

For example, in a first general synthetic procedure, azide or amine displacement of a leaving group alpha to the carbonyl group of the lactam leads

to the alpha-aminolactams. Such general synthetic procedures are exemplified by the introduction of a halogen atom followed by displacement with phthalimide anion or azide and subsequent conversion to the amine typically by hydrogenation for the azide as described in Rogriguez, et al., *Tetrahedron*, 52:7727-7736 (1996)³⁰, Parsons, et al., *Biochem. Biophys. Res. Comm.*, 117:108-113 (1983)³¹ and Watthey, et al., *J. Med. Chem.*, 28:1511-1516 (1985)³². One particular method involves iodination and azide displacement on, for example, benzylactams as described by Armstrong, et al., *Tetrahedron Lett.*, 35:3239 (1994)³³ and by King, et al., *J. Org. Chem.*, 58:3384 (1993)³⁴.

Another example of this first general procedure for the synthesis of alpha-aminolactams from the corresponding lactam involves displacement of a triflate group by an azido group as described by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995)³⁵.

Still another example of this first general procedure uses a Mitsunobu reaction of an alcohol and a nitrogen equivalent (either -NH₂ or a phthalimido group) in the presence of an azodicarboxylate and a triarylphosphine as described in Wada, et al., *Bull. Chem. Soc. Japan*, 46:2833-2835 (1973)³⁶ using an open chain reagent.

Yet another example of this first general procedure involves reaction of alpha-chlorolactams with anilines or alkyl amines in a neat mixture at 120°C to provide for 2-(N-aryl or N-alkyl)lactams as described by Gaetzi, *Chem. Abs.*, 66:28690m.³⁷

In a second general synthetic procedure, reaction of an enolate with an alkyl nitrite ester to prepare the alpha oxime followed by reduction yields the alpha-aminolactam compound. This general synthetic procedure is exemplified by Wheeler, et al., *Organic Syntheses*, Coll. Vol. VI, p. 840³⁸ which describes the reaction of isoamyl nitrite with a ketone to prepare the desired oxime. The

reduction of the oxime methyl ester (prepared from the oxime by reaction with methyl iodide) is described in the *J. Med. Chem.*, 28(12):1886 (1985)³⁹ and the reduction of alpha-oximino caprolactams by Raney-nickel and palladium catalysts is described by Brenner, et al., U.S. Patent No. 2,938,029.⁴⁰

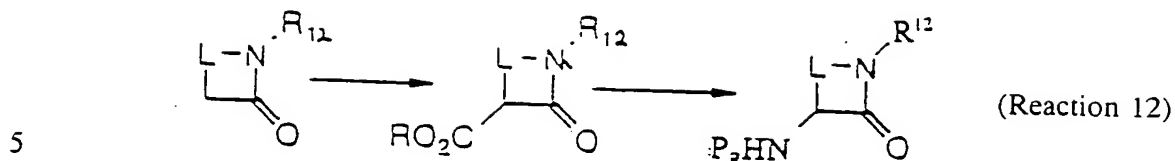
5

In a third general synthetic procedure, direct reaction of an enolate with an electrophilic nitrogen transfer agent can be used. The original reaction employed toluenesulfonyl azide but was improved as described by Evans, et al., *J. Am. Chem. Soc.*, 112:4011-4030 (1990)⁴¹. Specifically, direct introduction of an azido group which can be reduced to the amine by hydrogenation is described by Micouin, et al., *Tetrahedron*, 52:7719-7726 (1996)⁴². Likewise, the use of triisopropylbenzenesulfonyl azide as the azide transferring agent for reaction with an enolate is described by Evans, et al., *supra*. The use of triphenylphosphine to reduce the alpha-azidolactams to the corresponding aminolactams in the benzodiazepine series is disclosed by Butcher, et al., *Tetrahedron Lett.*, 37(37):6685-6688 (1996).⁴³ Lastly, diazo transfer of beta-diketones and subsequent reduction of the diazo group to the amino group is exemplified by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995)³⁵ who used Raney-nickel and hydrogen in acetic acid and acetic anhydride as the solvent.

20

In a fourth general procedure, N-substituted lactams are first converted to the 3-alkoxycarbonyl derivatives by reaction with a dialkyl carbonate and a base such as sodium hydride. See, for example, M.L. Reupple, et al., *J. Am. Chem. Soc.*, 93:7021 et seq. (1971)⁴⁴. The resulting esters serve as starting materials for conversion to the 3-amino derivatives. This conversion is achieved via the Curtius reaction as shown in reaction (12) below:

25



where Pr is as defined above and R¹² is typically hydrogen, an alkyl or an aryl group.

10

The Curtius reaction is described by P.A.S. Smith, *Organic Reactions*, 3:337-449 (1946).⁴⁵ Depending on the reaction conditions chosen, Pr = H or a protecting group such as Boc. For example, when R = H, treatment of the acid with diphenylphosphoryl azide in the presence of t-butanol provides the product wherein Pr = Boc.

15

The alpha-aminolactams employed as the cyclic amino compounds **2** in reaction (1) above include ring N-substituted lactams in addition to ring N-H lactams. Some methods for preparing ring N-substituted lactams have been described above. More generally, however, the preparation of these compounds range from the direct introduction of the substituent after lactam formation to essentially introduction before lactam formation. The former methods typically employ a base and an primary alkyl halide although it is contemplated that a secondary alkyl halide can also be employed although yields may suffer.

20

25

Accordingly, a first general method for preparing N-substituted lactams is achieved via reaction of the lactam with base and alkyl halide (or acrylates in some cases). This reaction is quite well known and bases such as sodamide, sodium hydride, LDA, LiHMDS in appropriate solvents such as THF, DMF, etc. are employed provided that the selected base is compatible with the

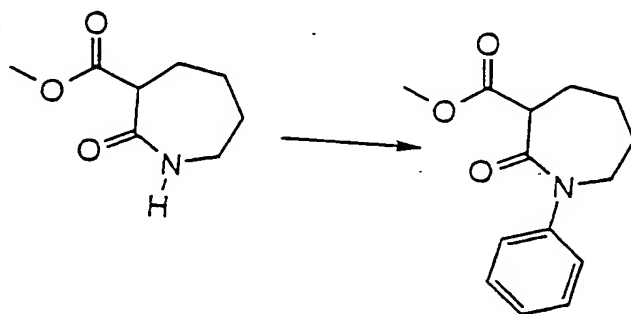
30

solvent. See for example: K. Orito, et al., *Tetrahedron*, 36:1017-1021 (1980)⁴⁶ and J.E. Semple, et al., *J. Med. Chem.*, 39:4531-4536 (1996)¹⁹ (use of LiHMDS with either R-X or acrylates as electrophiles).

5 A second general method employs reductive amination on an amino function which is then cyclized to an appropriate ester or other carbonyl function.

10 A third general method achieves production of the N-substitution during lactam formation. Literature citations report such production from either photolytic or thermal rearrangement of oxaziridines, particularly of N-aryl compounds. See, for example, Krimm, *Chem. Ber.*, 91:1057 (1958)⁴⁷ and Suda, et al., *J. Chem. Soc. Chem Comm.*, 949-950, (1994).⁴⁸ Also, the use of methyl hydroxylamine for the formation of nitrones and their rearrangement to the N-methyl derivatives is reported by Barton, et al., *J. Chem. Soc.*, 1764-1767 (1975).⁴⁹ Additionally, the use of the oxaziridine process in chiral synthesis has been reported by Kitagawa, et al., *J. Am. Chem. Soc.*, 117:5169-5178 (1975).⁵⁰

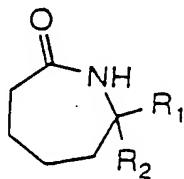
20 A more direct route to obtain N-phenyl substituted lactams from the corresponding NH lactams through the use of t-butyltetramethylguanidine and triphenylbismuth dichloride is disclosed by Akhatar, et al., *J. Org. Chem.*, 55:5222-5225 (1990)⁵¹ as shown in reaction (13) below.



(Reaction 13)

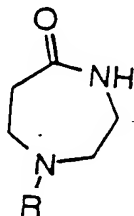
Given that numerous methods are available to introduce an alpha-amino group onto a lactam (or lactone) ring, the following lactams (and appropriate corresponding lactones) are contemplated for use in the synthesis of compounds of formula I above. Similar alcohol functions at the carbonyl position are derivative of either amine ring opening of cyclic epoxides, ring opening of aziridines, displacement of appropriate halides with amine or alcohol nucleophiles, or most likely reduction of appropriate ketones. These ketones are also of interest to the present invention.

Monocyclic lactams as described by Nedenskov, et al., *Acta Chem. Scand.*, 12:1405-1410 (1958)⁵² are represented by the formula:



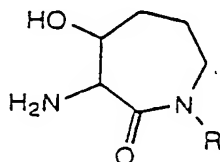
where R₁ and R₂ are exemplified by alkyl, aryl or alkenyl (e.g., allyl).

Monocyclic lactams containing a second nitrogen ring atom as described by Sakakida, et al., *Bull. Chem. Soc. Japan*, 44:478-480 (1971)⁵³ are represented by the formula:



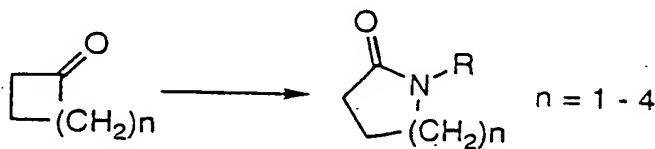
where R is exemplified by CH₃- or PhCH₂-.

Monocyclic lactams having hydroxyl substitution on the ring as described by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995)³⁵ are represented by the formula:



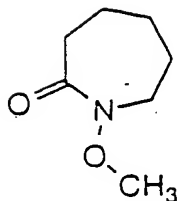
10 where R is exemplified by benzyl (includes both the cis and trans hydroxy lactams).

The direct preparation N-substituted lactams of 5-8 members from the corresponding ketones is described by Hoffman, et al., *Tet. Lett.*, 30:4207-4210 (1989).⁵⁴ These lactams are represented by the formula:

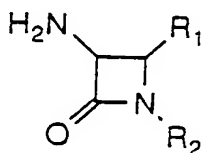


wherein R is alkyl, alkenyl, alkynyl, cycloalkyl, or benzyl.

25 N-Methoxylactams prepared from cyclohexanone and dimethoxyamine are described by Vedejs, et al., *Tet. Lett.*, 33:3261-3264 (1992).⁵⁵ These structures are represented by the formula:

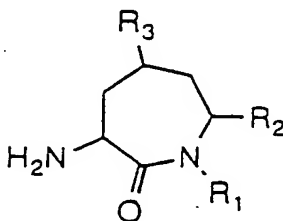


Substituted 3-aminoazetidinone derivatives prepared by a variety of routes including those described by van der Steen, et al., *Tetrahedron*, 47, 7503-7524 (1991)⁵⁶, Hart, et al., *Chem Rev.*, 89:1447-1465 (1989)⁵⁷ and references cited therein are represented by the formula:



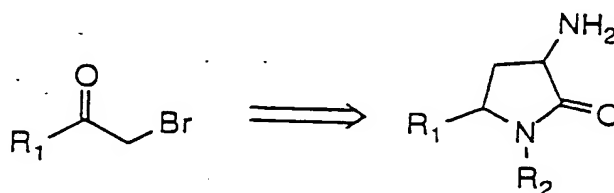
where R₁ and R₂ are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclic or are fused to form a cyclic group.

Ring substituted lactams are described by Lowe, et al., *Bioorg. Med. Chem. Lett.*, 4:2877-2882 (1994)⁵⁸ and are represented by the formula:



wherein R_2 and R_3 are exemplified by aryl and substituted aryl and R_1 is exemplified by alkyl or hydrogen.

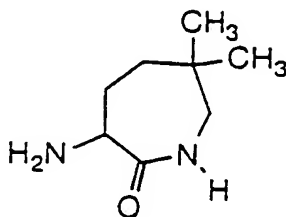
The synthesis of substituted 3-aminopyrrolidones from alpha-bromoketones is described by McKennis, Jr., et al., *J. Org. Chem.*, 28:383-387 (1963)⁵⁹. These compounds are represented by the formula:



where R^1 is aryl or heteroaryl and R^2 corresponds to any substituent for which the corresponding amine R^2-NH_2 exists.

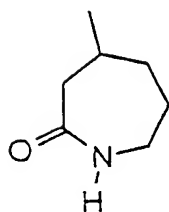
Additional references for the synthesis of alpha aminolactams are as follows:

1. Shirota, et al., *J. Med. Chem.*, 20:1623-1627 (1977)⁶⁰ which describes the synthesis of



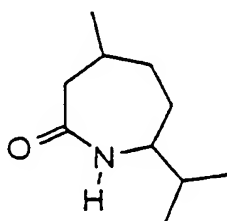
2. Overberger, et al., *J. Am. Chem. Soc.*, 85:3431 (1963)⁶¹ which describes the preparation of optically active β -methylcaprolactam of the formula:

5



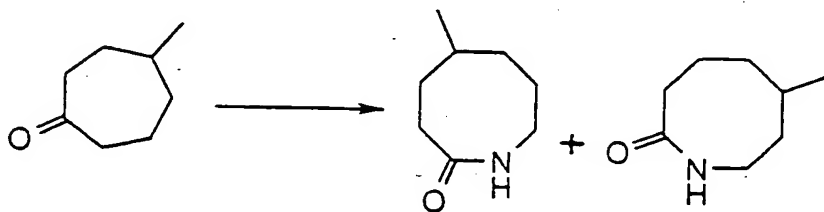
10 3. Herschmann, *Helv. Chim. Acta*, 32:2537 (1949)⁶² describes the synthesis of a disubstituted caprolactam from the Beckman rearrangement of menthone which is represented by the formula:

15

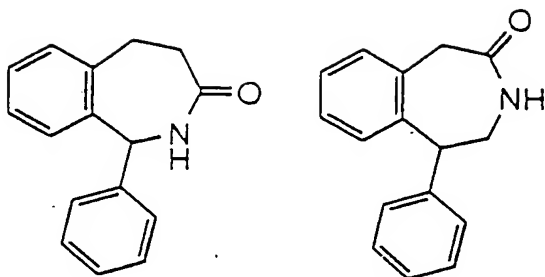


20 4. Overberger, et al., *Macromolecules*, 1:1 (1968)⁶³ describes the synthesis of eight-membered lactams from 3-methylcycloheptanone as shown below:

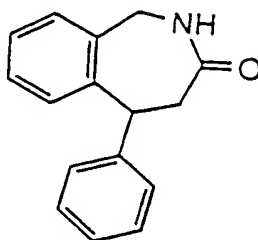
25



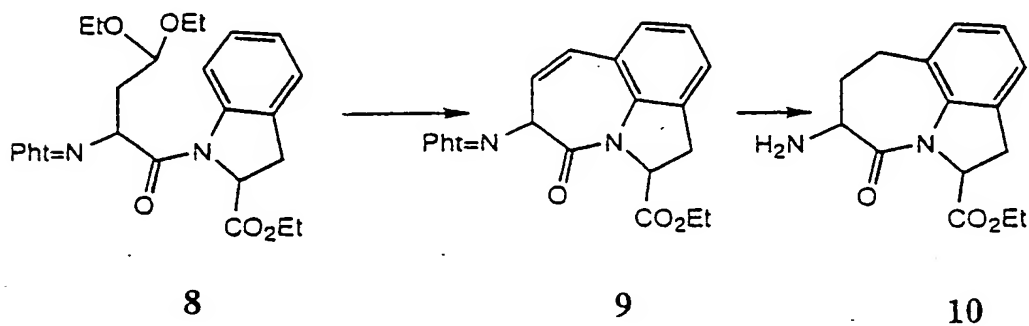
30 5. The synthesis of benzolactams (benzazepinones) has been reported by Busacca, et al., *Tet. Lett.*, 33:165-168 (1992)⁶⁴:



10

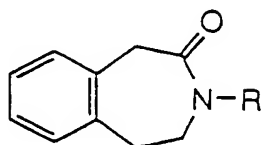


15



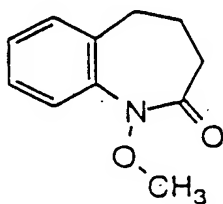
30

6. Orito, et al., *Tetrahedron*, 36:1017-1021 (1980)⁶⁸ discloses phenyl substituted benzazepinones represented by the formula:

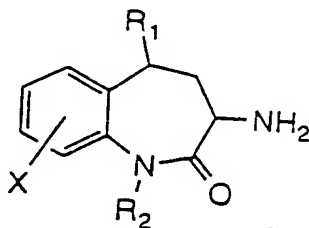


wherein R = H or CH₃-;

10 Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989)⁶⁹ discloses a N-methoxy benzazepinone represented by the formula:

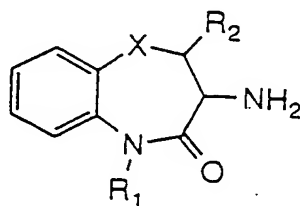


20 7. Lowe, et al., *J. Med. Chem.*, 37:3789-3811 (1994)⁷⁰ describes several synthetic pathways to substituted benzazepinones of the formula:



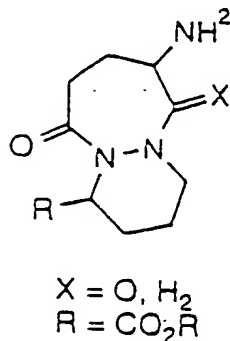
30 where R₁ is substituted aryl or cyclohexyl, X is a suitable substituent and R₂ can be H or alkyl. The syntheses described in Lowe are, however, adaptable to form numerous R¹ substituents.

8. Robl, et al., *Bioorg. Med. Chem. Lett.*, 4:1789-1794 (1994)⁷¹ and references cited therein as well as Skiles, et al., *Bioorg. Med. Chem. Lett.*, 3:773-778 (1993)⁷² disclose benzofused lactams which contain additional heteroatoms in the lactam ring. These compounds are represented by the formula:



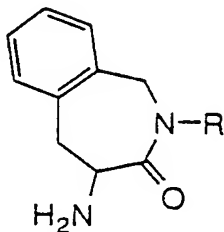
where X is O and R₂ = H or CH₃ or X = S and R₂ = H. In either case, R₁ = H or alkyl. Also, in Skiles, the thio group of the thiolactam can be oxidized to the SO₂ group. These structures are also presented from Beckmann rearrangement in Grunewald, et al., *J. Med. Chem.*, 39(18):3539 (1996).⁷³

9. Also syntheses for the benzoheterolactam series is presented in Thomas, et al., *J. Chem. Soc., Perkin II*, 747 (1986)⁷⁴ which could lead to compounds of the formula:



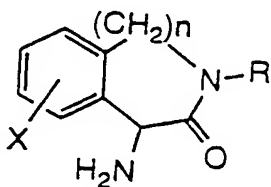
where X is O or H₂ and R is CO₂R.

10. Further examples of benzazepinones are found in Warshawsky, et al., *Bioorg. Med. Chem. Lett.*, 6:957-962 (1996)⁷⁵ which discloses



The synthesis can be generalized to produce R = alkyl or aryl.

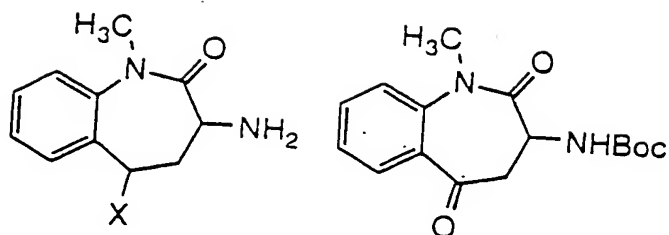
11. Ben-Ishai, et al., *Tetrahedron*, 43:439-450 (1987)⁷⁶ describes syntheses which could lead to several benzolactams of the formula



wherein n = 0,1,2 and R = -CH₃, PhCH₂- and H.

12. van Niel et al., *Bioorg. Med. Chem. Lett.*, 5:1421-1426 (1995)⁷⁷ reports the synthesis of

5

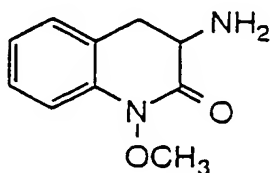


10

wherein X is -OH, -NH₂ or -NR⁶R⁶ where R⁶ is as defined above. The reported ketone is a versatile synthetic intermediate which can be modified by conventional methods such as reductive amination, reduction, etc.

15

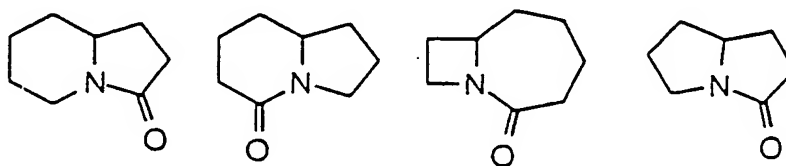
13. Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989)⁷⁸ describes a synthetic method for the preparation of:



20

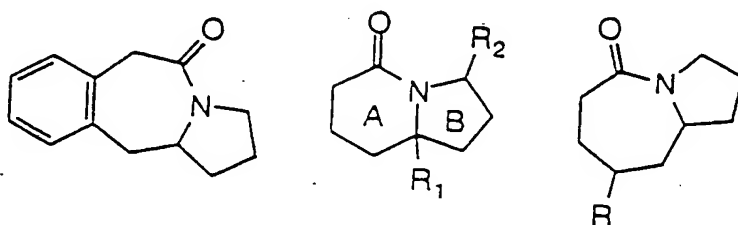
In addition to the above, saturated bicyclic alpha-aminolactams are also contemplated for use in the synthesis of compounds of formula I. Such saturated bicyclic alpha-aminolactams are well known in the art. For example, Edwards, et al., *Can. J. Chem.*, 49:1648-1658 (1971)⁷⁹ describes several syntheses of bicyclic lactams of the formula:

25



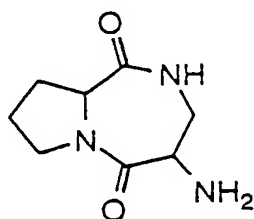
30

Similarly, Milligan, et al., *J. Am. Chem. Soc.*, 117:10449-10459 (1995)⁸⁰ and references cited therein report the synthesis of lactams of the formula:

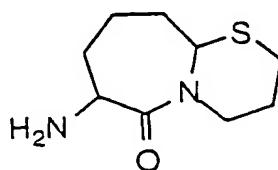


wherein R_1 and R_2 are H or $-CH_3$, ring A can have from 6-13 members and ring B can have from 5 - 7 members. R can be alkyl, aryl, cycloalkyl, and the like.

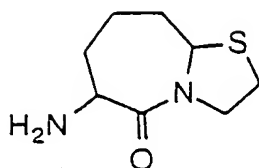
The introduction of a heteroatom into the saturated cyclic structure fused to the lactam ring is disclosed by Curran et al., *Tet. Lett.*, 36:191-194 (1995)⁸¹ who describe a synthetic method which can be used to obtain a lactam of the formula:



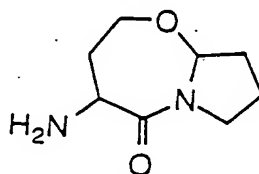
by Slusarchyk, et al., *Bioorg. Med. Chem. Lett.*, 5:753-758 (1995)⁸² who describe syntheses which could lead to a lactam of the formula:



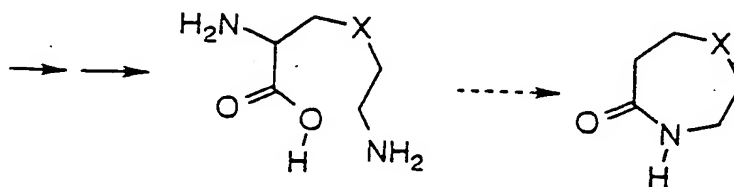
and by Wyvratt, et al., Eur. Pat. Appl. 61187 (1982)⁸³ who describe a lactam of the formula:



10 Lactams having further heteroatom(s) in the cyclic lactam structure (in addition to the nitrogen of the amido group of the lactam) are described by Cornille, et al., *J. Am. Chem. Soc.*, 117:909-917 (1995)⁸⁴ who describe lactams of the formula:

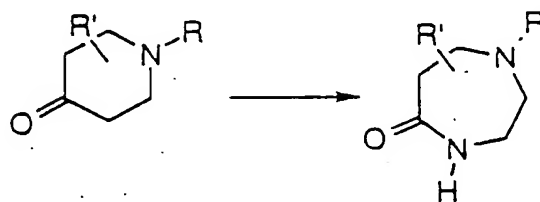


20 J. Kolc, *Coll. Czech. Chem. Comm.*, 34:630 (1969)⁸⁵ who describes lysines suitable for cyclization to lactams which have a hetero lactam ring atom as shown by the formula:



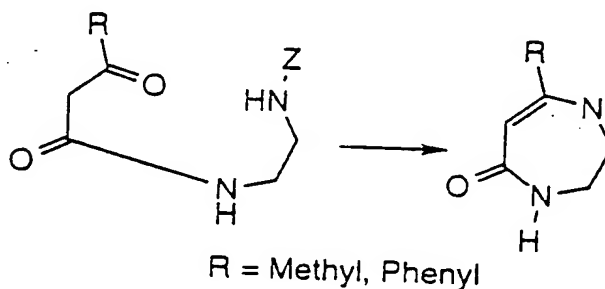
30 where X=O, S and NR where R is, for example, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic, and the like.

Similarly, each of Dickerman, et al., *J. Org. Chem.*, 14:530 (1949)⁸⁶,
Dickerman, et al., *J. Org. Chem.*, 20:206 (1955)⁸⁷, and Dickerman, et al., *J.*
Org. Chem., 19:1855 (1954)⁸⁸ used the Schmidt and Beckmann reactions on
substituted 4-piperidones to provide for lactams of the formula:



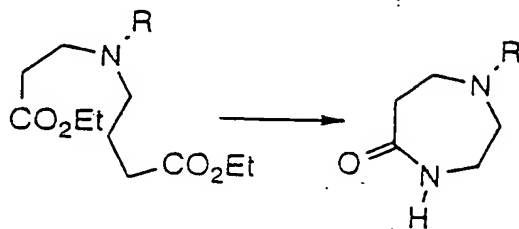
where R is acyl, alkyl, substituted alkyl, aryl, heteroaryl or heterocyclic
provided that R is not an acid labile group such as t-Boc; and R' is hydrogen,
alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, heteroaryl,
heteroaryloxy, heterocyclic, heterocycloxy, halo, cyano, nitro, trihalomethyl,
and the like.

An internal cyclization of appropriate ethylenediamine amides onto a
ketone or aldehyde is described by Hoffman, et al., *J. Org. Chem.*, 27:3565
(1962)⁸⁹ as follows:



Ring expansion methodology based on beta lactams to provide for larger
ring lactams containing an aza group has twice been reported in Wasserman, et
al., *J. Am. Chem. Soc.*, 103:461-2 (1981)⁹⁰ and in Crombie, et al., *Tetrahedron*
Lett., 27(42):5151-5154 (1986).⁹¹

Dieckmann methodology has been used to prepare aza caprolactams from unsymmetrical amines such as shown below by Yokoo, et al., *Bull. Chem. Soc. Jap.*, 29:631 (1956).⁹²

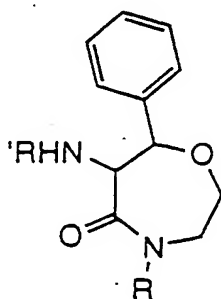


where R is as defined in this reference. The disclosure of Yokoo, et al. can be extended to cover R being alkyl, substituted alkyl, aryl, alkoxy, substituted alkoxy, heteroaryl, cycloalkyl, heterocyclic, alkenyl, substituted alkenyl, and the like.

15

The synthesis of various members of the oxalactam series has been reported by Burkholder, et al., *Bioorg. Med. Chem. Lett.*, 2:231 (1993)⁹³ and references cited therein which oxalactams are represented by the formula:

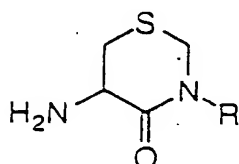
20



where 'R is as defined in the reference and R can be alkyl, substituted alkyl, aryl, alkoxy, substituted alkoxy, heteroaryl, cycloalkyl, heterocyclic, alkenyl, substituted alkenyl, and the like.

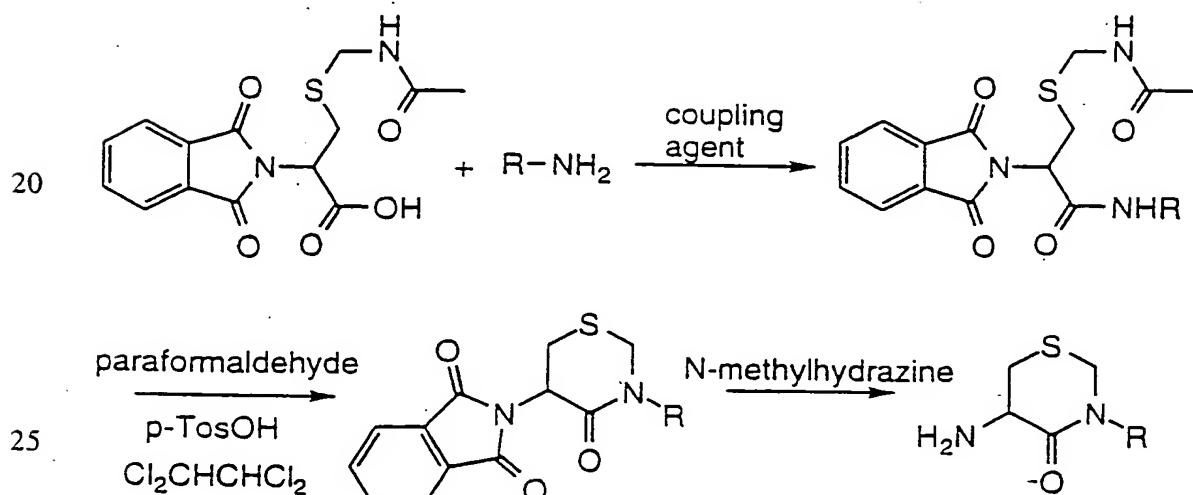
30

The synthesis of thialactams (generally oxalactams can be made by the same methodology) has been reported by Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982)¹⁸ who prepared thialactams of the formula:



This reference provides a series of procedures having broad application for synthesis of lactams permitting R in the above formula to be derived from any amine (alkyl, aryl, heteroaryl, etc.) with the restriction being that the R-group does not contain any functional groups reactive with formaldehyde (e.g., primary and secondary amines). The general synthetic scheme provided by Freidlinger, et al. is:

15

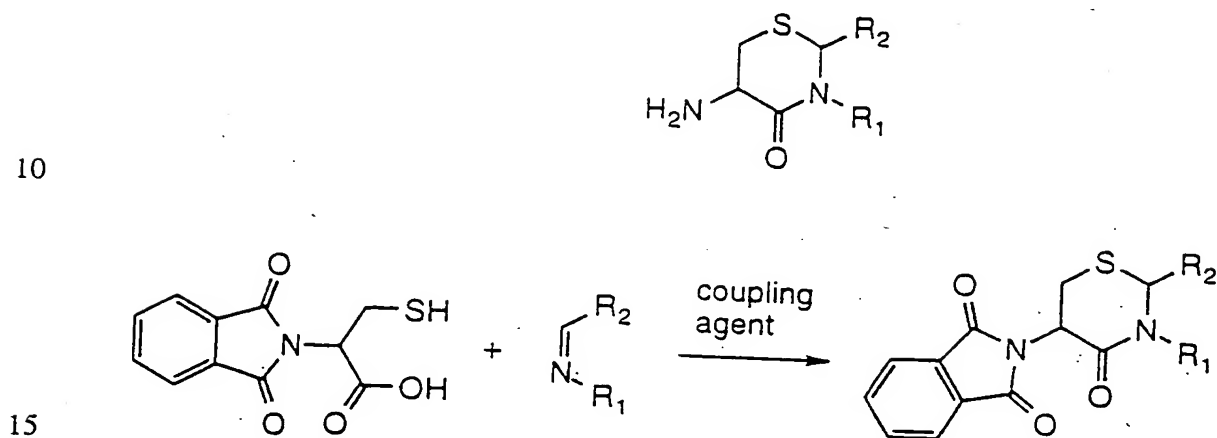


The coupling agent is any standard reagent used in the formation of typical peptide or amide bonds, for example, carbodiimide reagents. See, also,

30

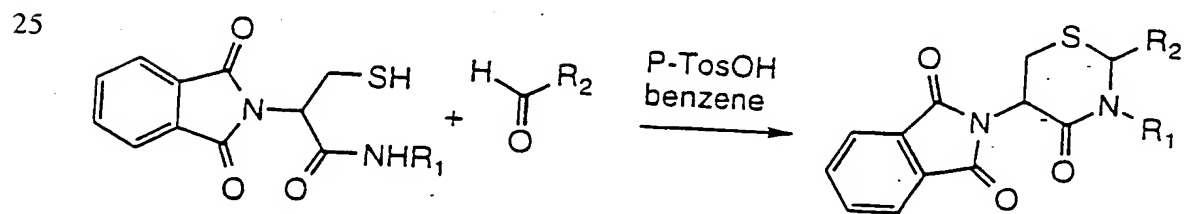
Karanewsky, U.S. Patent No. 4,460,579⁹⁴ and Kametani, et al., *Heterocycles*, 9:831-840 (1978).⁹⁵

The Friedinger procedure can be extended to afford disubstituted thialactams of the following structure:



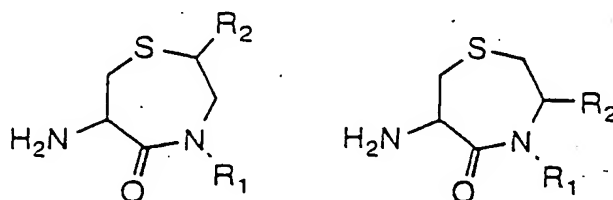
In practical terms, R_2 will be limited to aryl and heteroaryl groups and sterically hindered alkyl groups such as t-butyl. R_1 can be highly variable and is limited only by subsequent reaction steps.

Still further is the Kametani procedure which provides for lactams as follows:

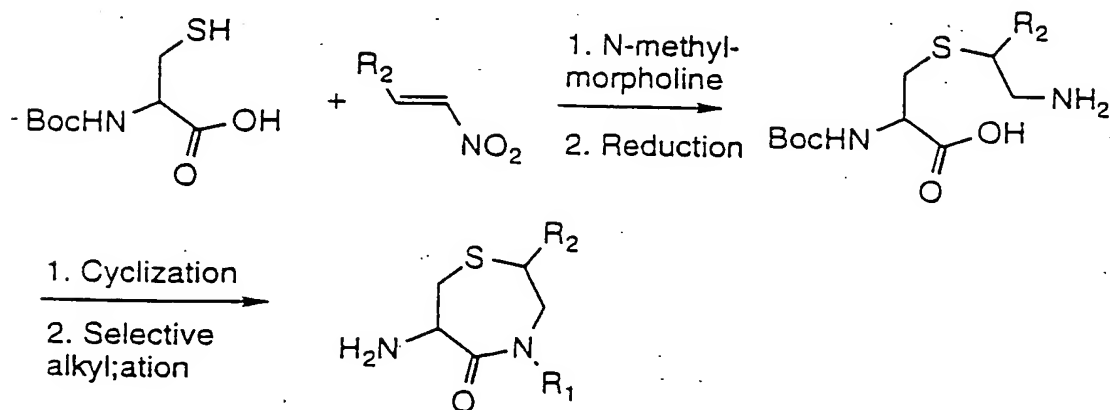


In principle, the Kametani procedure allows for a wide selection of R1 and R2 groups limited primarily by stability to the reaction conditions.

See, for example, Yanganasawa, et al., *J. Med. Chem.*, 30:1984-1991 (1987)⁹⁶ and J. Das et al., *Biorg. Med. Chem. Lett.*, 4:2193-2198 (1994)⁹⁷ which describes general methods for the synthesis of isomeric 7-membered thialactams of the following structure:

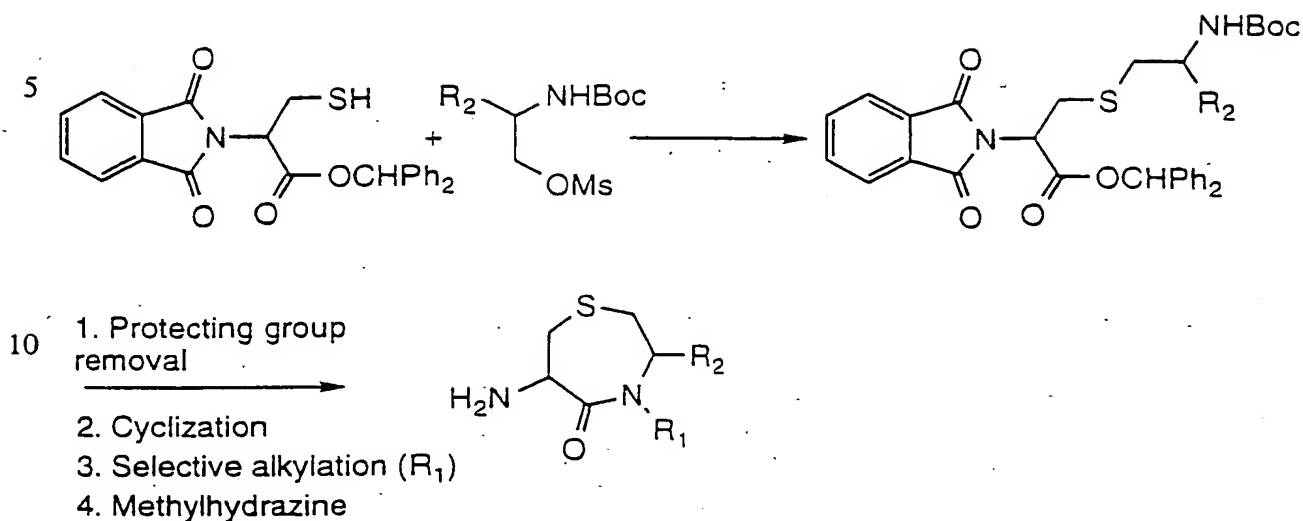


The first synthetic route is:



R₂ can be highly variable (e.g., alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic and the like) since a number of well documented routes exist for the synthesis of nitroethylene derivatives from aldehydes and nitromethane (Henry reaction) followed by dehydration. R₁ is limited to groups that can undergo alkylation reactions.

The second compound series can be prepared as follows:



- 15 In this synthesis, R_2 can be highly variable. The starting component required to introduce R_2 can be readily derived by the reduction of any known alpha-BOC-amino acid to the alcohol derivative followed by formation of the mesylate.

As noted above, the primary approaches to the preparation of lactams is the Beckmann/Schmidt ring expansion reaction using either inter- or intramolecular approaches serves to prepare lactams of various ring sizes. The intramolecular approach generates bicyclic materials with the lactam nitrogen incorporated into the ring fusion. Additional approaches set forth above are at the base of the methodology are internal cyclization of omega-amino acids/esters where the construction of the substituent pattern takes place prior to cyclization, and internal cyclization of an electrophilic center onto a nucleophilic functional group as in the Friedel Crafts type cyclization at the center of the Ben-Ishal procedure for making benzazepinones. This latter procedure is applicable to a wide variety of heteroaromatics as well as benzenoid rings, and may also be applied to non-aromatic double or triple bonds to generate a wide array of substituents or ring fusions.

Deoxygenation of the lactam by reagents such as diborane, LiAlH_4 , and the like leads to azaheterocycles ($=\text{X}$ is dihydro).

Similarly, for $\text{X} = \text{H}$, OH , such compounds can be prepared by
5 epoxidation of cycloalkenyl groups followed by oxirane opening by, e.g., ammonia. After formation of compounds of formula I, $=\text{X}$ being H , OH can be oxidized to provide for cycloalkylones ($=\text{X}$ being oxo).

Additionally, the 5,7-dihydro-6H-diben[b,d]azepin-6-one derivatives
10 employed in this invention can be prepared using conventional procedures and reagents. For example, an appropriately substituted *N-tert*-Boc-2-amino-2'-methylbiphenyl compound can be cyclized to form the corresponding 5,7-dihydro-6H-diben[b,d]azepin-6-one derivative by first treating the biphenyl compound with about 2.1 to about 2.5 equivalents of a strong base, such as sec-
15 butyl lithium. This reaction is typically conducted at a temperature ranging from about -80°C to about -60°C in an inert diluent such as THF. The resulting dianion is then treated with dry carbon dioxide at a temperature of about -78°C to afford the 5,7-dihydro-6H-diben[b,d]azepin-6-one. This procedure is described further in R. D. Clark et al., *Tetrahedron*, **49**(7), 1351-
20 1356 (1993) and references cited therein.

After forming the 5,7-dihydro-6H-diben[b,d]azepin-6-one, the amide nitrogen can be readily alkylated by first treating the dibenazepinone with about 1.1 to about 1.5 equivalents of a strong base, such as sodium hydride, in an
25 inert diluent, such as DMF. This reaction is typically conducted at a temperature ranging from about -10°C to about 80°C for about 0.5 to about 6 hours. The resulting anion is then contacted with an excess, preferably about 1.1 to about 3.0 equivalents, of an alkyl halide, typically an alkyl chloride, bromide or iodide. Generally, this reaction is conducted at a temperature of
30 about 0°C to about 100°C for about 1 to about 48 hours.

An amino group can then be introduced at the 5-position of the 7-alkyl-5,7-dihydro-6H-diben[b,d]azepin-6-one using conventional procedures and reagents. For example, treatment of 7-methyl-5,7-dihydro-6H-diben[b,d]azepin-6-one with an excess of butyl nitrite in the presence of a
5 strong base, such as potassium 1,1,1,3,3,3-hexamethyldisilazane (KHMDs), affords 5-oximo-7-methyl-5,7-dihydro-6H-diben[b,d]azepin-6-one. Subsequent reduction of the oximo group by hydrogenation in the presence of a catalyst, such as palladium on carbon, then provides 5-amino-7-methyl-5,7-dihydro-6H-diben[b,d]azepin-6-one. Other conventional amination procedures, such as
10 azide transfer followed by reduction of the azido group, may also be employed.

Similarly, various benzodiazepine derivatives suitable for use in this invention can be prepared using conventional procedures and reagents. For example, a 2-aminobenzophenone can be readily coupled to α -(isopropylthio)-
15 N-(benzyloxycarbonyl)glycine by first forming the acid chloride of the glycine derivative with oxalyl chloride, and then coupling the acid chloride with the 2-aminobenzophenone in the presence of a base, such as 4-methylmorpholine, to afford the 2-[α -(isopropylthio)-N-(benzyloxycarbonyl)glyciny]-aminobenzophenone. Treatment of this compound with ammonia gas in the
20 presence of an excess, preferably about 1.1 to about 1.5 equivalents, of mercury (II) chloride then affords the 2-[N-(α -amino)-N'-(benzyloxycarbonyl)glyciny]aminobenzophenone. This intermediate can then be readily cyclized by treatment with glacial acetic acid and ammonium acetate to provide the 3-(benzyloxycarbonyl)amino-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one1.
25 Subsequent removal of the Cbz group affords the 3-amino-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one.

Alternatively, 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-ones can be readily aminated at the 3-position using conventional azide transfer reactions
30 followed by reduction of the resulting azido group to form the corresponding amino group. The conditions for these and related reactions are described in

the examples set forth below. Additionally, 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-ones are readily alkylated at the 1-position using conventional procedures and reagents. For example, this reaction is typically conducted by first treating the benzodiazepinone with about 1.1 to about 1.5 equivalents of a
5 base, such as sodium hydride, potassium *tert*-butoxide, potassium 1,1,1,3,3,3-hexamethyldisilazane, cesium carbonate, in an inert diluent, such as DMF. This reaction is typically conducted at a temperature ranging from about -78°C to about 80°C for about 0.5 to about 6 hours. The resulting anion is then contacted with an excess, preferably about 1.1 to about 3.0 equivalents, of an
10 alkyl halide, typically an alkyl chloride, bromide or iodide. Generally, this reaction is conducted at a temperature of about 0°C to about 100°C for about 1 to about 48 hours.

Additionally, the 3-amino-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-
15 benzodiazepines employed in this invention are typically prepared by first coupling malonic acid with a 1,2-phenylenediamine. Conditions for this reaction are well known in the art and are described, for example, in PCT Application WO 96-US8400 960603. Subsequent alkylation and amination using conventional procedures and reagents affords various 3-amino-1,5-
20 bis(alkyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines. Such procedures are described in further detail in the example set forth below.

Accordingly, a vast number of lactams, lactones and thiolactones are available by art recognized procedures. Similarly, the art is replete with
25 examples of aminocycloalkyl compounds for use in the synthesis of compounds of formula I above.

In the synthesis of compounds of formula I using the synthetic methods described above, the starting materials can contain a chiral center (e.g., alanine)
30 and, when a racemic starting material is employed, the resulting product is a mixture of R,S enantiomers. Alternatively, a chiral isomer of the starting

material can be employed and, if the reaction protocol employed does not racemize this starting material, a chiral product is obtained. Such reaction protocols can involve inversion of the chiral center during synthesis.

5 Accordingly, unless otherwise indicated, the products of this invention are a mixture of R,S enantiomers. Preferably, however, when a chiral product is desired, the chiral product corresponds to the L-amino acid derivative. Alternatively, chiral products can be obtained via purification techniques which separates enantiomers from a R,S mixture to provide for one or the other
10 stereoisomer. Such techniques are well known in the art.

Pharmaceutical Formulations

 When employed as pharmaceuticals, the compounds of formula I are usually administered in the form of pharmaceutical compositions. These
15 compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

20 This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an
25 excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid
30 or in a liquid medium), ointments containing, for example, up to 10% by

weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

5 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation,
10 e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose,
15 polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release
20 of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each
25 dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with
30 a suitable pharmaceutical excipient. Preferably, the compound of formula I above is employed at no more than about 20 weight percent of the

pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

5 The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual
10 patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid
15 preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type
20 described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged
25 action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can
30 be used for such enteric layers or coatings, such materials including a number

of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate the pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

5

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
10	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

15 The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

20 A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>
25	Active Ingredient	5
	Lactose	95

30 The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

5	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
10	Polyvinylpyrrolidone	
	(as 10% solution in sterile water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
15	Total	120 mg

20 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

30 Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
35	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

5

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

10

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

15

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

20

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

25

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
30 Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

35

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in

water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

5

Formulation Example 8

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	15.0 mg
10	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

15 The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

20 A subcutaneous formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1.0 mg
25	corn oil	1 ml

(Depending on the solubility of the active ingredient in corn oil, up to about 5.0 mg or more of the active ingredient may be employed in this formulation, if desired).

30

Formulation Example 10

A topical formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1-10 g
35	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

5

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

10

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

15

20

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

25

30

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

5 Utility

The compounds and pharmaceutical compositions of the invention are useful in inhibiting β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in diagnosing and treating Alzheimer's disease in mammals including humans.

10

As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to enhance the *in vivo* serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

15

20

The amount of compound administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from AD in an amount sufficient to at least partially arrest further onset of the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the judgment of the attending clinician depending upon factors such as the degree or severity of AD in the patient, the age, weight and general condition of the patient, and the like.

25

30

Preferably, for use as therapeutics, the compounds described herein are administered at dosages ranging from about 1 to about 500 mg/kg/day.

5 In prophylactic applications, compositions are administered to a patient at risk of developing AD (determined for example by genetic screening or familial trait) in an amount sufficient to inhibit the onset of symptoms of the disease. An amount adequate to accomplish this is defined as "prophylactically effective dose." Amounts effective for this use will depend on the judgment of the attending clinician depending upon factors such as the age, weight and general
10 condition of the patient, and the like. Preferably, for use as prophylactics, the compounds described herein are administered at dosages ranging from about 1 to about 500 mg/kg/day.

As noted above, the compounds administered to a patient are in the form of
15 pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be
20 between 3 and 11, more preferably from 5 to 9 and most preferably from 7 and 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The compounds described herein are also suitable for use in the
25 administration of the compounds to a cell for diagnostic and drug discovery purposes. Specifically, the compounds may be used in the diagnosis of cells releasing and/or synthesizing β -amyloid peptide. In addition the compounds described herein are useful for the measurement and evaluation of the activity of other candidate drugs on the inhibition of the cellular release and/or
30 synthesis of β -amyloid peptide.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

5 In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

10	BEMP	=	2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
	Boc	=	<i>t</i> -butoxycarbonyl
	BOP	=	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
	bd	=	broad doublet
15	bs	=	broad singlet
	d	=	doublet
	dd	=	doublet of doublets
	DIC	=	diisopropylcarbodiimide
	DMF	=	dimethylformamide
20	DMAP	=	dimethylaminopyridine
	DMSO	=	dimethylsulfoxide
	EDC	=	ethyl-1-(3-dimethylaminopropyl)carbodiimide
	eq.	=	equivalents
	EtOAc	=	ethyl acetate
25	g	=	grams
	HOBt	=	1-hydroxybenzotriazole hydrate
	Hunig's base	=	diisopropylethylamine
	L	=	liter
	m	=	multiplet
30	M	=	molar
	max	=	maximum
	meq	=	milliequivalent
	mg	=	milligram
	mL	=	milliliter
35	mm	=	millimeter
	mmol	=	millimole
	MOC	=	methoxyoxycarbonyl
	N	=	normal
	N/A	=	not available
40	ng	=	nanogram
	nm	=	nanometers
	OD	=	optical density
	PEPC	=	1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide

	PP-HOBT	=	piperidine-piperidine-1-hydroxybenzotrizole
	psi	=	pounds per square inch
	ϕ	=	phenyl
5	q	=	quartet
	quint.	=	quintet
	rpm	=	rotations per minute
	s	=	singlet
	t	=	triplet
	TFA	=	trifluoroacetic acid
10	THF	=	tetrahydrofuran
	tlc	=	thin layer chromatography
	μ L	=	microliter
	UV	=	ultra-violet

15 In the examples below, all temperatures are in degrees Celcius (unless otherwise indicated). The compounds set forth in the examples below were prepared using the following general procedures as indicated.

20 In the following examples and procedures, the term "Aldrich" indicates that the compound or reagent used in the procedure is commercially available from Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA; the term "Fluka" indicates that the compound or reagent is commercially available from Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA; the term "Lancaster" indicates that the
25 compound or reagent is commercially available from Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA; the term "Sigma" indicates that the compound or reagent is commercially available from Sigma, P.O. Box 14508, St. Louis MO 63178 USA; the term "Chemservice" indicates that the compound or reagent is commercially available from Chemservice Inc.,
30 Westchester, PA; the term "Bachem" indicates that the compound or reagent is commercially available from Bachem Biosciences Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA; the term "Maybridge" indicates that the compound or reagent is commercially available from Maybridge Chemical Co. Trevillet, Tintagel, Cornwall PL34 OHW
35 United Kingdom; and the term "TCI" indicates that the compound or reagent is commercially available from TCI America, 9211 North Harborage Street,

Portland OR 97203; the term "Alfa" indicates that the compound or reagent is commercially available from Johnson Matthey Catalog Company, Inc. 30 Bond Street, Ward Hill, MA 01835-0747; the term "Novabiochem" indicates that the compound or reagent is commercially available from Calbiochem-Novabiochem Corp. 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087; the term "Oakwood" indicates that the compound or reagent is commercially available from Oakwood, Columbia, South Carolina; the term "Advanced Chemtech" indicates that the compound or reagent is commercially available from Advanced Chemtech, Louisville, KY; and the term "Pfaltz & Bauer" indicates that the compound or reagent is commercially available from Pfaltz & Bauer, Waterbury, CT, USA.

I. Coupling Procedures

15. GENERAL PROCEDURE A

First EDC Coupling Procedure

To a 1:1 mixture of the corresponding carboxylic acid and the corresponding amino acid ester or amide in CH_2Cl_2 at 0°C was added 1.5 equivalents triethylamine, followed by 2.0 equivalents hydroxybenzotriazole monohydrate and then 1.25 equivalents of ethyl-3-(3-dimethylamino)propyl carbodiimide-HCl. The reaction mixture was stirred overnight at room temperature and then transferred to a separatory funnel. The mixture was washed with water, saturated aqueous NaHCO_3 , 1N HCl and saturated aqueous NaCl, and then dried over MgSO_4 . The resulting solution was stripped free of solvent on a rotary evaporator to yield the crude product.

GENERAL PROCEDURE B

Second EDC Coupling Procedure

A mixture of the corresponding acid (1 eqv), N-1-hydroxybenzotriazole (1.6 eqv), the corresponding amine (1 eqv), N-methylmorpholine (3 eqv) and dichloromethane (or DMF for insoluble substrates) was cooled in an ice-water

bath and stirred until a clear solution was obtained. EDC (1.3 eqv) was then added to the reaction mixture. The cooling bath was then allowed to warm to ambient temperature over 1-2 h and the reaction mixture was stirred overnight. The reaction mixture was then evaporated to dryness under vacuum. To the
5 residue was added 20% aqueous potassium carbonate and the mixture was shaken thoroughly and then allowed to stand until the oily product solidified (overnight if necessary). The solid product was then collected by filtration, washed thoroughly with 20% aqueous potassium carbonate, water, 10% HCl, and water to give the product, usually in pure state. No racemization was
10 observed.

GENERAL PROCEDURE C

Third EDC Coupling Procedure

The carboxylic acid was dissolved in methylene chloride. The
15 corresponding amino acid ester or amide (1 eq.), N-methylmorpholine (5 eq.) and hydroxybenzotriazole monohydrate (1.2 eq.) were added in sequence. A cooling bath was applied to the round bottomed flask until the solution reached 0°C. At that time, 1.2 eq. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added. The solution was allowed to stir overnight and come
20 to room temperature under nitrogen pressure. The reaction mixture was worked up by washing the organic phase with saturated aqueous sodium carbonate, 0.1M citric acid, and brine before drying with sodium sulfate. The solvents were then removed to yield crude product.

25

GENERAL PROCEDURE D

Fourth EDC Coupling Procedure

A round bottom flask was charged with the corresponding carboxylic acid (1.0 eq.), hydroxybenzotriazole hydrate (1.1 eq.) and the corresponding amine (1.0 eq.) in THF under nitrogen atmosphere. An appropriate amount (1.1 eq for
30 free amines and 2.2 eq. for hydrochloride amine salts) of base, such as Hunig's base was added to the well stirred mixture followed by EDC (1.1 eq.). After

stirring from 4 to 17 hours at room temperature the solvent was removed at reduced pressure, the residue taken up in ethyl acetate (or similar solvent) and water, washed with saturated aqueous sodium bicarbonate solution, 1 N HCl, brine, dried over anhydrous sodium sulfate and the solvent removed at reduced pressure to provide the product.

GENERAL PROCEDURE E

BOP Coupling Procedure

To a stirred solution of *N*-(3,5-difluorophenylacetyl)alanine (2 mmol) in DMF, cooled in an ice-water bath, was added BOP (2.4 mmol) and *N*-methylmorpholine (6 mmol). The reaction mixture was stirred for 50 min. and then a solution of α -amino- γ -lactam (2 mmol) in DMF cooled at 0 °C was added. The cooling bath was allowed to warm to ambient temperature over 1-2 h and the reaction mixture was then stirred overnight. A 20% aqueous potassium carbonate solution (60 mL) was added and this mixture shaken thoroughly. No solid formed. The mixture was then washed with ethyl acetate (150 mL) and evaporated to dryness under vacuum to give a white solid. Water (50 mL) was then added and this mixture shaken thoroughly. The precipitate that formed was collected by filtration, then washed thoroughly with water, followed by 1 mL of diethyl ether to give the product (51 mg, 0.16 mmol, 7.8%).

GENERAL PROCEDURE F

Coupling of an Acid Chloride with an Amino Acid Ester

To a stirred solution of (D,L)-alanine isobutyl ester hydrochloride (4.6 mmol) in 5 ml of pyridine was added 4.6 mmol of the acid chloride. Precipitation occurred immediately. The mixture was stirred for 3.5 h, dissolved in 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated to yield the product. Other amino acid esters may also be employed in this procedure.

GENERAL PROCEDURE G

Coupling of a Carboxylic Acid with an Amino Acid Ester

A solution of the carboxylic acid (3.3 mmol) and 1,1'-carbodiimidazole (CDI) in 20 mL THF was stirred for 2 h. (D,L)-alanine isobutyl ester
5 hydrochloride (3.6 mmol) was added, followed by 1.5 mL (10.8 mmol) of triethylamine. The reaction mixture was stirred overnight. The reaction mixture was dissolved in 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated to yield the product.
10 Other amino acid esters may also be employed in this procedure.

GENERAL PROCEDURE H

Fifth EDC Coupling Procedure

In a round bottom flask was added a carboxylic acid (1.1 eq.) in THF, an
15 amine hydrochloride (1.0 eq.), 1-hydroxybenzotriazole hydrate (1.1 eq.), N,N-diisopropylethylamine (2.1 eq.), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.1 eq.). The reaction mixture stirred at room temperature for 10-20 hours under an atmosphere of nitrogen. The mixture was diluted with EtOAc and washed with 0.1 M HCl (1 x 10 mL),
20 saturated NaHCO₃ (1 x 10 mL), H₂O (1 x 10 mL), and brine and dried over MgSO₄. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel followed by trituration from EtOAc and hexanes.

25

GENERAL PROCEDURE I

Sixth EDC Coupling Procedure

To a solution or suspension of the amine or amine hydrochloride (1.0 eq.) in THF (0.05-0.1 M) under N₂ at 0°C was added the carboxylic acid (1.0-1.1 eq.), hydroxybenzotriazole monohydrate (1.1-1.15 eq.), Hunig's base (1.1 eq. for
30 free amines and 1.1-2.3 eq. for hydrochloride amine salts), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1-1.15 eq.). The

cooling bath was removed and the mixture allowed to warm to room temperature for 10-24 hours. The solution or mixture was diluted with EtOAc, in a 3-5 volume multiple of the initial THF volume, and washed with 0.1-1.0 M aq. HCl (1 or 2x), dilute NaHCO₃ (1 or 2x), and brine (1x). Then, the organic phase was dried over either MgSO₄ or Na₂SO₄, filtered, concentrated to provide the crude product, which was either further purified or utilized without further purification.

GENERAL PROCEDURE J

10

EEDQ Coupling Procedure

To a solution of the amine in THF (1.0 eq., 0.05-0.08 M, final molarity) under N₂ at room temperature was added the N-t-Boc protected amino acid (1.1 eq., either as a solid or in THF via cannula), followed by EEDQ (Aldrich, 1.1 eq.). The pale yellow solution was stirred at room temperature for 16-16.5 hours, then diluted with EtOAc (in a 3-5 volume multiple of the initial THF volume), and washed with 1M aq. HCl (2x), dilute aq. NaHCO₃ (2x), and brine (1x). The organic phase was dried over either Na₂SO₄ or MgSO₄, filtered, and concentrated.

20

II. Carboxylic Acids

GENERAL PROCEDURE II-A

Ester Hydrolysis to Free Acid

Ester hydrolysis to the free acid was conducted by conventional methods. Below are two examples of such conventional de-esterification methods.

Method A: To a carboxylic ester compound in a 1:1 mixture of CH₃OH/H₂O was added 2-5 equivalents of K₂CO₃. The mixture was heated to 50°C for 0.5 to 1.5 hours until tlc showed complete reaction. The reaction was cooled to room temperature and the methanol was removed on a rotary evaporator. The pH of the remaining aqueous solution was adjusted to ~2, and

ethyl acetate was added to extract the product. The organic phase was then washed with saturated aqueous NaCl and dried over MgSO₄. The solution was stripped free of solvent on a rotary evaporator to yield the product.

5 Method B: The amino acid ester was dissolved in dioxane/water (4:1) to which was added LiOH (~2 eq.) that was dissolved in water such that the total solvent after addition was about 2:1 dioxane:water. The reaction mixture was stirred until reaction completion and the dioxane was removed under reduced pressure. The residue was dissolved in water and washed with ether. The layers
10 were separated and the aqueous layer was acidified to pH 2. The aqueous layer was extracted with ethyl acetate. The ethyl acetate extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure after filtration. The residue was purified by conventional methods (e.g., recrystallization).

15. GENERAL PROCEDURE II-B

Acid Chloride Preparation

3,5-Difluorophenylacetic acid (30 g, 0.174 mol) (Aldrich) was dissolved in dichloromethane and this solution was cooled to 0°C. DMF (0.5 mL, catalytic) was added followed by the dropwise addition of oxalyl chloride (18 mL, 0.20 mol) over a 5 minute period. The reaction was stirred for 3 h and then rotoevaporated at reduced pressure to give an oil which was placed on a high vacuum pump for 1 h to afford 3,5-difluorophenylacetyl chloride as a thin yellow oil. Other acid chlorides can be prepared in a similar manner.

25 GENERAL PROCEDURE II-C

Schotten-Baumann Procedure

3,5-Difluorophenylacetyl chloride (from General Procedure II-B) was added dropwise to a 0°C solution of L-alanine (Aldrich) (16.7 g, 0.187 mol) in 2 N sodium hydroxide (215 mL, 0.43 mol). The reaction was stirred for 1 h at 0°C and then overnight at room temperature. The reaction was diluted with water (100 mL), then extracted with ethyl acetate (3 x 150 mL). The organic layer

was then washed with brine (200 mL), dried over MgSO_4 , and rotoevaporated at reduced pressure to a residue. Recrystallization of the residue from ethyl acetate/hexanes afforded the desired product (34.5 g, 82% yield). Other acid chlorides may be used in this procedure to provide for intermediates useful in this invention.

GENERAL PROCEDURE II-D

Reductive Amination

To a solution of the arylamine in ethanol in a hydrogenation flask was added 1 equivalent of the 2-oxocarboxylic acid ester (e.g., pyruvate ester), followed by 10% palladium on carbon (25 weight percent based on the arylamine). The reaction was hydrogenated at 20 psi H_2 on a Parr shaker until complete reaction was indicated by tlc (30 minutes to 16 hours). The reaction mixture was then filtered through a pad of Celite 545 (available from Aldrich Chemical Company, Inc.) and stripped free of solvent on a rotary evaporator. The crude product residue was then further purified via chromatography.

Example A

Synthesis of N-(Phenylacetyl)-L-alanine

Using General Procedure II-C, the title compound was prepared from phenylacetyl chloride (Aldrich) and L-alanine (Aldrich) as a solid having a melting point of 102-104°C.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 9.14 (br s, 1H), 7.21-7.40 (m, 5H), 6.20 (d, J = 7.0 Hz, 1H), 4.55 (m, 1H), 3.61 (s, 2H), 1.37 (d, J = 7.1 Hz, 3H).

^{13}C -nmr (CDCl_3): δ = 176.0, 171.8, 134.0, 129.4, 127.5, 48.3, 43.2, 17.9.

Example B

Synthesis of N-(3,5-Difluorophenylacetyl)-L-alanine

Using General Procedure II-C, the title compound was prepared from 3,5-difluorophenylacetyl chloride (General Procedure II-B) and L-alanine (Aldrich).

NMR data was as follows:

¹H-nmr (CD₃OD): δ = 8.32 (br s, 0.3H), 6.71 (m, 2H), 6.60 (m, 1H), 4.74 (br s, 1.7H), 4.16 (m, 1H), 3.36 (s, 2H), 1.19 (d, J = 7.3 Hz, 3H).

¹³C-nmr (CD₃OD): δ = 175.9, 172.4, 164.4 (dd, J = 13.0, 245.3 Hz), 141.1, 113.1 (dd, J = 7.8, 17.1 Hz), 102.9 (t, J = 25.7 Hz), 49.5, 42.7, 17.5.

Example C

10

Synthesis of N-(Cyclopentylacetyl)-L-phenylglycine

Step A - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine Methyl Ester

Following General Procedure A above using cyclopentylacetic acid (Aldrich) and phenylglycine methyl ester hydrochloride (Novabiochem), the title compound was prepared as a solid having a melting point of 83-86°C. The reaction was monitored by tlc on silica gel (R_f = 0.28 in 25% ethyl acetate/hexanes) and purification was by recrystallization from ethyl acetate/hexanes.

15

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35 (s, 5H), 6.44 (bd, 1H), 5.6 (d, 1H), 3.72 (s, 3H), 2.24 (bs, 3H), 1.9-1.4 (m, 6H), 1.2-1.05 (m, 2H).

20

¹³C-nmr (CDCl₃): δ = 172.3, 171.7, 136.7, 129.0, 128.6, 127.3, 56.2, 52.7, 42.5, 36.9, 32.40, 32.38, 24.8.

C₁₆H₂₁NO₃ (MW = 275.35); mass spectroscopy (M+Na) 298.

25

Step B - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine

Following General Procedure II-A above using N-(cyclopentylacetyl)-L-phenylglycine methyl ester (from Step A), the title compound was prepared as a solid having a melting point of 155-158°C. The reaction was monitored by tlc on silica gel (R_f = 0.18 in 10% methanol/dichloromethane).

30

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 8.60 (d, J = 7.8 Hz, 1H), 7.45 (m, 5H), 5.41 (d, J = 7.2 Hz, 1H), 2.20 (m, 3H), 1.8-1.1 (m, 8H).

^{13}C -nmr (CDCl_3): δ = 172.3, 172.0, 137.5, 128.7, 128.1, 127.8, 56.2, 40.9, 36.8, 31.8, 24.5.

5 $\text{C}_{15}\text{H}_{19}\text{NO}_3$ (MW = 261.32); mass spectroscopy (M+Na) 284.

Example D

Synthesis of N-(Cyclopentylacetyl)-L-alanine

Step A - Preparation of N-(Cyclopentylacetyl)-L-alanine Methyl Ester

10 Following General Procedure A above using cyclopentylacetic acid (Aldrich) and L-alanine methyl ester hydrochloride (Sigma), the title compound was prepared as a solid having a melting point of 43-46°C. Purification was by recrystallization from ethyl acetate/hexanes.

NMR data was as follows:

15 ^1H -nmr (CDCl_3): δ = 6.38 (d, 1H), 4.50 (m, 1H), 3.65 (s, 3H), 2.13 (bs, 3H), 1.80-1.00 (m (includes d at 1.30, 3H), 11H).

^{13}C -nmr (CDCl_3): δ = 173.7, 172.5, 52.1, 47.6, 42.3, 36.8, 32.15, 32.14, 18.0.

20 $\text{C}_{11}\text{H}_{19}\text{NO}_3$ (MW = 213.28); mass spectroscopy (MH^+) 214.

Step B - Preparation of N-(Cyclopentylacetyl)-L-alanine

25 Following General Procedure II-A above using N-(cyclopentylacetyl)-L-alanine methyl ester (from Step A), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.18 in 10% methanol/dichloromethane).

NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): δ = 12.45 (bs, 1H), 8.12 (d, J =7.2 Hz, 1H), 4.24 (quint, J = 7.2 Hz, 1H), 2.14 (m, 3H), 1.8-1.4 (m, 6H), 1.29 (d, J = 7.2 Hz, 3H), 1.2-1.0 (m, 3H).

30 ^{13}C -nmr ($\text{DMSO}-d_6$): δ = 174.6, 171.9, 47.3, 41.1, 36.7, 31.8, 24.5, 17.2.

$\text{C}_{10}\text{H}_{17}\text{NO}_3$ (MW = 199.25); mass spectroscopy (MH^+) N/A.

Example E

Synthesis of N-(Cyclopropylacetyl)-L-alanine

Step A - Preparation of N-(Cyclopropylacetyl)-L-alanine Methyl Ester

Following General Procedure A above using cyclopropylacetic acid
5 (Aldrich) and L-alanine methyl ester hydrochloride (Sigma), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.15 in 25% ethyl acetate/hexanes) and purification was by flash column chromatography using 25% ethyl acetate/hexanes as the eluant.

NMR data was as follows:

10 ^1H -nmr (CDCl_3): δ = 6.60 (d, 1H), 4.55 (m, 1H), 3.69 (s, 3H), 2.10 (m, 2H), 1.34 (d, 3H), 0.95 (m, 1H), 0.58 (m, 2H), 0.15 (m, 2H).
 ^{13}C -nmr (CDCl_3): δ = 173.7, 172.3, 52.3, 47.7, 41.0, 18.2, 6.7, 4.27, 4.22.
 $\text{C}_9\text{H}_{15}\text{NO}_3$ (MW = 185.22); mass spectroscopy (MH^+) N/A.

15 Step B - Preparation of N-(Cyclopentylacetyl)-L-alanine

Following General Procedure II-A above using N-(cyclopropylacetyl)-L-alanine methyl ester (from Step A), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.27 in 10% methanol/dichloromethane).

20 NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): δ = 8.18 (d, 1H), 4.25 (m, 1H), 2.08 (m, 2H), 1.30 (d, 3H), 1.00 (m, 1H), 0.50 (m, 2H), 0.19 (m, 2H).

^{13}C -nmr ($\text{DMSO}-d_6$): δ = 174.6, 171.7, 47.4, 17.3, 7.6, 4.12, 4.06.

$\text{C}_8\text{H}_{13}\text{NO}_3$ (MW = 199.25); mass spectroscopy (MH^+) N/A.

25

Example F

Synthesis of N-(Cyclopropylacetyl)-L-phenylglycine

Step A - Preparation of N-(Cyclopropylacetyl)-L-glycine Methyl Ester

Following General Procedure A above using cyclopropylacetic acid
30 (Aldrich) and L-phenylglycine methyl ester, the title compound was prepared as a solid having a melting point of 74-76°C. The reaction was monitored by tlc

on silica gel ($R_f = 0.61$ in 50% ethyl acetate/hexanes) and purification was by recrystallization from ethyl acetate/hexanes.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.35$ (m, 5H), 6.97 (bd, $J=7.2$ Hz, 1H), 5.59 (d, $J=7.8$ Hz, 1H), 3.71 (s, 3H), 2.17 (m, 2H), 1.05-0.95 (m, 1H), 0.62 (m, 2H), 0.20 (m, 2H).

^{13}C -nmr (CDCl_3): $\delta = 171.9, 174.6, 136.6, 129.0, 128.5, 127.2, 56.1, 52.7, 41.0, 6.9, 4.37, 4.33$.

$\text{C}_{14}\text{H}_{17}\text{NO}_3$ (MW = 247.30); mass spectroscopy (MH^+) N/A.

Step B - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine

Following General Procedure II-A above using N-(cyclopropylacetyl)-L-phenylglycine methyl ester (from Step A), the title compound was prepared as a solid having melting point of 152-157°C. The reaction was monitored by tlc on silica gel ($R_f = 0.23$ in 10% methanol/dichloromethane) and purification was by recrystallization from ethyl acetate/hexanes.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 8.47$ (d, $J = 7.69$ Hz, 1H), 7.35 (m, 5H), 5.34 (d, $J = 7.69$ Hz, 1H), 2.10 (m, 2H), 0.90 (m, 1H), 0.40 (m, 2H), 0.10 (m, 2H).

^{13}C -nmr (CDCl_3): $\delta = 172.3, 171.8, 137.6, 128.7, 56.2, 7.7, 4.0$.

$\text{C}_{13}\text{H}_{15}\text{NO}_3$ (MW = 233.27); mass spectroscopy (MH^+) N/A.

Example H

Synthesis of N-(2-Biphenyl)-D,L-alanine

2-Aminobiphenyl (2 g, 11.8 mmol, Aldrich), triethylamine (1.2 eq.) and ethyl 2-bromopropionate (1.1 eq., Aldrich) were combined and heated to 85°C with stirring. After 7 days, the mixture was diluted with chloroform and washed with water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography (1:1 CH_2Cl_2 /hexanes). The resulting oil was dissolved in a 1:2 mixture of water/dioxane (200 mL) and LiOH (2 eq.) was added. After 2 hours, the mixture was concentrated to yield

an oil which was dissolved in water. The aqueous solution was washed with ether then was adjusted to pH 3 with 5N HCl and extracted with ethyl acetate. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography (EtOAc) to yield the title compound.

5

Example I

Synthesis of N-(Phenyl-furazan-3-yl)-D,L-alanine

Following General Procedure II-D and using 4-phenyl-furazan-3-ylamine (Maybridge) and ethyl pyruvate (Aldrich), the ethyl ester was prepared. Following General Procedure II-A, Method B (LiOH/H₂O/dioxane) and using the ethyl ester, the title compound was prepared.

15

Example L

Synthesis of S-(+)-3,5-Difluoromandelic Acid

Step A - Preparation of Methyl S-(±)-3,5-difluoromandelate

To a solution of 3,5-difluorobenzaldehyde (Aldrich) in CH₂Cl₂ (100 mL) was added ZnCl₂ (6.7 g, 21.1 mmol) to form a slurry. Trimethylsilyl cyanide (21.0 g, 211.2 mmol) dissolved in CH₂Cl₂ (100 mL) was slowly added to the slurry at 0°C. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was then diluted with water and the organic layer separated. The combined organic layers were concentrated to a residue. The residue was dissolved with MeOH (200 mL) at 0°C and anhydrous HCl gas bubbled into the solution for 10 min. After stirring at room temperature for 18 h, the solution was concentrated to a solid. The solid was dissolved in CH₂Cl₂ / H₂O and the aqueous portion extracted with CH₂Cl₂. The combined organics were washed with brine, dried over anhydrous MgSO₄ and concentrated to a solid (37.4 g, 87.6%), mp = 77-78°C.

¹H NMR (300 MHz, CDCl₃): δ = 6.97 (dd, J = 9.6 Hz, J = 1.79 Hz, 2H), 6.74 (dt, J = 8.82, J = 2.28 Hz, 1H), 5.14 (d, J = 4.64 Hz, 1H), 3.78 (s, 3H), 3.54 (d, J = 5.1 Hz, 1H).

30

Step B - Preparation of Methyl S-(+)-3,5-difluoromandellate

Methyl (\pm)-3,5-difluoromandellate was separated via preparative chiral HPLC to give a white solid having a melting point of 70-71°C.

$C_9H_8F_2O_3$ (MW = 202.17); mass spectroscopy found ($M+NH_4^+$) 220.0.

5 Anal. calcd for $C_9H_8F_2O_3$: C, 53.47; H, 3.99. Found: C, 53.40; H, 3.89.

Step C - Preparation of S-(+)-3,5-Difluoromandelic acid

A solution of methyl S-(+)-3,5-difluoromandellate (1 eq.) in 74% aqueous THF was cooled to 0 °C and treated with lithium hydroxide. After 40 minutes
10 at 0 °C the reaction was complete by TLC. The contents were transferred to a separatory funnel and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was acidified with 0.5 N $NaHSO_4$ and extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried
15 over Na_2SO_4 , filtered, and concentrated to a white solid having a melting point of 119-122 °C. The 1H NMR was consistent with known 3,5-difluoromandelic acid.

Example M

Synthesis of

20 **2-Azido-(3,5-difluorophenyl)acetic Acid**

Step A: To a three-necked flask equipped with a mechanical stirrer and a nitrogen inlet tube was added 3,5-difluorophenylacetic acid and THF. The reaction mixture was cooled to -78°C and 1.2 eq. of triethylamine was added, followed by dropwise addition of trimethylacetyl chloride (1.05 eq.). During the
25 addition, the temperature was maintained at -78°C. The cold bath was then removed and replaced with an ice bath. The temperature was allowed to warm to 0°C and stirring was continued for 1 hour. The reaction mixture was then re-cooled to -78°C. To a second flask charged with THF, triphenylmethane (cat, 0.1 mole %) and (S)-(-)-4-benzyl-2-oxazolidione (1.1 eq.) (Aldrich) at -78°C
30 was added an n-butyl lithium solution dropwise until an orange color persisted. This reaction mixture was stirred at -78°C for 30 min. and then cannulated into the first reaction mixture. The resulting mixture was allowed to stir at -78°C for

1 hour and then quenched with 2.2 eq. of acetic acid. The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane and this solution washed with water, followed by 1M potassium carbonate. The organic layer was then dried over sodium sulfate, filtered and concentrated. The residue was purified by LC 2000 chromatography, eluting with EtOAC/Hexane (15:85). The resulting oil was slurried in hexane to afford a white solid which was collected by filtration to give (S)-(-)-3-(3,5-difluorophenylacetyl)-4-benzyl-2-oxazolidione.

Step B: To (S)-(-)-3-(3,5-difluorophenylacetyl)-4-benzyl-2-oxazolidione (3.0 mM) in 20 mL of dry THF cooled to -78°C was added LiHMDS (1.05 eq.) dropwise while maintaining the temperature at -78°C. The reaction mixture was allowed to stir at -78°C for 15 min. and then a pre-cooled (-60°C) solution of trisyl azide (1.12 eq.) in 10 mL of THF was added. The reaction mixture was allowed to stir an additional 10 min. and then was quenched with 4.4 eq. of acetic acid. Using a warm water bath, the temperature was raised to 30-40°C for 6 hrs. The reaction mixture was then poured into a separatory funnel and extracted into dichloromethane. The organic layer was washed with bicarbonate solution, followed by brine, and then dried over sodium sulfate, filtered and solvent removed. The residue was purified by LC 2000 chromatography to afford methyl 2-azido-2-(3,5-difluorophenyl)acetate.

Step C: To a solution of methyl 2-azido-2-(3,5-difluorophenyl)acetate in THF/H₂O (2.6:1) cooled to 0°C was added 1.7 eq. of lithium hydroxide. The reaction mixture was stirred at room temperature for 3 hours and then poured into a separatory funnel. The mixture was extracted into water and washed with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was then washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2-azido-2-(3,5-difluorophenyl)acetic acid.

Example N

Synthesis of
(R)-N,N'-Di-BOC-2-Hydrazinopropionic Acid

5 Step A: To (S)-(-)-4-benzyl-2-oxazolidanone (Aldrich) in THF cooled to -50°C was added n-butyl lithium 1.1 eq. (1.6 M in hexane) dropwise. The reaction mixture was allowed to warm to -20°C and then was re-cooled to -78°C and propionyl chloride (1.1 eq) was added in one portion. The reaction mixture was allowed to stir an additional 15 min. at -78°C and then was allowed to warm to room temperature. The reaction was then quenched with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic
10 extracts were washed with water, followed by brine and then dried over sodium sulfate, filtered and concentrated to give (S)-(-)-3-propionyl-4-benzyl-2-oxazolidanone.

15 Step B: To a solution of (S)-(-)-3-propionyl-4-benzyl-2-oxazolidanone in THF at -78°C was added KHMDS (1.05 eq.) (Aldrich) dropwise. The reaction mixture was allowed to stir at -78°C for 30 min. and then a precooled solution of di-tert-butyl-azodicarboxylate (Aldrich) was added via a cannula. After 5 min. 2.6 eq. of acetic acid was added. The reaction mixture was then extracted
20 with dichloromethane and the organic layer was washed with 1M potassium phosphate. The organic layer was then dried over sodium sulfate, filtered and concentrated to give (S)-(-)-3-[(R)-N,N'-di-BOC-2-hydrazinopropionyl]-4-benzyl-2-oxazolidanone.

25 Step C: To (S)-(-)-3-[(R)-N,N'-di-BOC-2-hydrazinopropionyl]-4-benzyl-2-oxazolidanone (0.49 moles) at 0°C in 8 mL of THF and 3 mL of water was added LiOH (1.7 eq.) and H₂O₂ (3.0 eq.) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then poured into a separatory funnel and diluted with water. The aqueous mixture was extracted
30 with ethyl acetate and then acidified to pH 2.0 with 1N HCl and extracted with ethyl acetate. The organic layer was then dried over sodium sulfate, filtered and

solvent removed to give (R)-N,N'-di-BOC-2-hydrazinopropionic acid which was used without further purification.

Example O

**Synthesis of
3,5-Difluorophenyl- α -oxoacetic Acid**

Step A: Ethyl 3,5-difluorophenyl- α -oxoacetate was prepared from 1-bromo-3,5-difluorobenzene (Aldrich) according to the procedure described in *J. Org. Chem.*, 45 (14), 2883-2887 (1980).

Step B: Ethyl 3,5-difluorophenyl- α -oxoacetate was hydrolyzed using General Procedure II-A (Method B) to afford 3,5-difluorophenyl- α -oxoacetic acid.

Example P

**Synthesis of
Cyclopentyl- α -hydroxyacetic Acid**

The title compound (CAS No. 6053-71-0) was prepared in two steps from cyclopentylmethanal (CAS No. 872-53-7, Wiley) using the procedure described by Gibby, W. A.; Gubler, C. J. *Biochemical Medicine* 1982, 27, 15-25.

Example Q

Synthesis of N-(3,4-dichlorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859, the disclosure of which is incorporated herein by reference in its entirety, N-(3,4-dichlorophenyl)alanine was prepared. Specifically, to a solution of 3,4-dichloroaniline (1 equivalent) (Aldrich) in isopropanol (about 500 mL per mole of 3,4-dichloroaniline) is added water (about 0.06 mL per mL of isopropanol) and 2-chloropropionic acid (2 equivalents) (Aldrich). This mixture is warmed to 40°C and sodium bicarbonate (0.25 equivalents) is added in successive portions before heating under reflux for 4-5 days. After cooling, the reaction mixture is poured into water and the unreacted 3,4-dichloroaniline is removed by filtration.

The filtrate is acidified to pH 3-4 with concentrated hydrochloric acid and the resultant precipitate is filtered, washed and dried to yield the title compound, m.p. = 148-149°C.

5

Example R

Synthesis of N-(3,5-difluorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859 and Example Q above, N-(3,5-difluorophenyl)alanine was prepared using 3,5-difluoroaniline (Aldrich) and 2-chloropropionic acid (Aldrich).

10

Example S

Synthesis of

α -Fluoro-3,5-difluorophenylacetic Acid

Step A - Synthesis of Methyl 3,5-Difluoromandelate

15

To a solution of 3,5-difluoromandelic acid (Fluorochem) in methanol was bubbled HCl gas for 10 minutes. The reaction was refluxed overnight. The mixture was then concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated to give the title intermediate as a white solid.

20

C₉H₈F₂O₃ (MW=202.17); mass spectroscopy 202.

¹H NMR (300 MHz, CDCl₃): δ = 7.00 (2H, d, J=6.58 Hz), 6.76 (1H, t, J=8.86 Hz), 5.16 (1H, d, J=5.29 Hz), 3.81 (3H, s), 3.54 (1H, d, J=5.39 Hz).

25

Step B - Synthesis of Methyl α -Fluoro-3,5-difluorophenylacetate

A solution of diethylaminosulfur trifluoride (DAST) (1.1 eq) in methylene chloride was cooled to 0°C and a pre-cooled solution of methyl 3,5-difluoromandelate (1 eq) in methylene chloride was added. The transfer flask was rinsed with a small portion of methylene chloride. After 15 minutes, the cooling bath was removed and the reaction mixture was stirred an additional 40 minutes at ambient temperature. The mixture was poured over ice and the layers separated. The organic phase was washed with saturated NaHCO₃ and

30

brine. The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC eluting with 7% ethyl acetate/hexanes providing the title intermediate as a yellow oil.

$\text{C}_9\text{H}_7\text{F}_3\text{O}_2$ (MW=204.16); mass spectroscopy 204.

Anal. calcd for $\text{C}_9\text{H}_7\text{F}_3\text{O}_2$: C, 52.95; H, 3.46. Found: C, 52.80; H, 3.73.

Step C - Synthesis of α -Fluoro-3,5-difluorophenylacetic Acid

Following General Procedure II-A, Method B and using methyl α -fluoro-3,5-difluorophenylacetate, the title intermediate was prepared as a white solid having a melting point of 100-102°C.

$\text{C}_8\text{H}_5\text{F}_3\text{O}_2$ (MW = 190.13); mass spectroscopy 190.

Anal. calcd for $\text{C}_8\text{H}_5\text{F}_3\text{O}_2$: C, 50.54; H, 2.65. Found: C, 50.47; H, 2.79.

III. Cycloalkyl, Lactam, Lactone and Related Compounds

1. Cycloalkane Derivatives

Example 1-1

**Synthesis of
1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
aminodibenzosuberane**

Following General Procedure C above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 1-aminodibenzosuberane, the title compound was prepared. The product was purified by chromatography (silica, 2.5% MeOH/ CHCl_3), followed by recrystallization from *n*-chlorobutane/acetonitrile.

NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): δ = 4.53 (m, 1H), 6.37 (d, 1H).

$\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_2\text{F}_2$ (MW = 434.48); mass spectroscopy (MH^+) 434.

2. Cyclic Alcohol Derivatives

Example 2-A

Synthesis of
5-Amino-5,7-dihydro-6H-
dibenzo[a,c]cyclohepten-6-ol Hydrochloride

5 Step A - Synthesis of 5-Oximo-5,7-dihydro-6H-
 dibenzo[a,c]cyclohepten-6-one

A round bottom flask was charged with 5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one (1.0 g, 4.81 mmol)(CAS# 1139-82-8, prepared as described in *Tetrahedron Letters*, Vol. 28, No. 23, (1987), pp 2633-2636) and butyl nitrite (0.673 ml, 5.77 mmol) (Aldrich) in Et₂O. The solution was cooled to 0°C and treated drop-wise with a saturated solution of HCl(g)/Et₂O. After 5 h at 0°C the resulting precipitate was filtered, rinsed with cold Et₂O and vacuum dried to give the title compound as a colorless solid.

NMR data was as follows:

15 ¹H-nmr (CDCl₃): δ = 7.26-7.74 (m, 8H), 3.84 (m, 2H).

C₁₅H₁₁NO₂ (MW = 237.26); mass spectroscopy (MH⁺) 238.

Anal. Calcd for C₁₅H₁₁NO₂; C, 75.93 H, 4.67 N, 5.90. Found: C, 75.67 H, 4.83 N, 5.67.

20 Step B- Synthesis of 5-Amino-5,7-dihydro-6H-
 dibenzo[a,c]cyclohepten-6-ol Hydrochloride

The compound isolated above (0.489 g, 2.04 mmol) was dissolved in THF and added drop-wise to a well-stirred mixture of LAH (10.2 ml, 10.2 mmol)/THF. After heating to reflux for 25 h under N₂ atmosphere the solution was quenched and worked-up according to Fieser's method. The resulting solid was rinsed with NH₃ sat/CHCl₃, the filtrate evaporated and the title compound purified by chromatography (SiO₂, CHCl₃).

C₁₅H₁₅NO (MW = 225.290); mass spectroscopy (MH⁺) 226.

30 Anal. Calcd for C₁₅H₁₅NO; C, 79.97 H, 6.71 N, 6.22. Found: C, 80.19 H, 6.71 N, 5.91.

Example 2-1

**Synthesis of
1-(R)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino-2-(S)-indanol**

5 Following General Procedure C and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 1-(R)-amino-2-(S)-indanol, the title compound was prepared.

Example 2-2

10 **Synthesis of
1-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino-2-(R)-indanol**

 Following the General Procedure C and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 1-(S)-amino-2-(R)-indanol, the title compound was
15 prepared.

Example 2-3

20 **Synthesis of
1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino-2-indanol**

 Following General Procedure C and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 1-amino-2-indanol, the title compound was prepared.

Example 2-4

25 **Synthesis of
trans-2-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino-1-cyclohexanol**

 Following General Procedure C above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and *trans*-2-aminocyclohexanol hydrochloride (Aldrich),
30 the title compound was prepared as a solid having a melting point of 189-191°C. The reaction was monitored by tlc on silica gel ($R_f = 0.85$ in 9% methanol/dichloromethane) and purification was by flash chromatography using 9% methanol/dichloromethane as the eluant.

 NMR data was as follows:

¹H-nmr (CD₃OD): δ = 6.8-6.6 (m, 3H), 4.1 (m, J = 7.2 Hz, 1H), 3.4 (m, 4H), 3.1 (m, 1H), 1.8-1.4 (m, 4H), 1.1 (m, 7H).

¹³C-nmr (CD₃OD) δ = 175.4, 173.0, 113.9, 113.6, 103.9, 103.6, 74.3, 56.9, 51.4, 51.4, 50.4, 43.4, 43.3, 43.31, 36.0, 35.5, 32.9, 32.8, 26.2, 26.2, 25.9, 25.8, 18.8, 18.7.

C₁₇H₂₂N₂O₃F₂ (MW = 340.37); mass spectroscopy (MH⁺) 341.

Example 2-5

Synthesis of

1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)- amino-1,2,3,4-tetrahydro-2-naphthol

Following General Procedure C and using using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 1-amino-1,2,3,4-tetrahydro-2-naphthol, the title compound was prepared.

Example 2-6

Synthesis of

1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)- aminobenz[f]cycloheptan-2-ol

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and *cis*-1-amino-2-hydroxybenzosuberane (prepared using the procedure described in C. H. Senanayake et al., *Tetrahedron Lett.* (1995) 36(42), 7615-7618), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.4 in 10% methanol/dichloromethane) and purification was by silica gel chromatography using 10% methanol/dichloromethane as the eluant.

NMR data was as follows:

Mixture of *cis* isomers:

¹H-nmr (DMSO-d₆): δ = 4.46 (m, 1H), 5.05 (d, 1H).

C₂₂H₂₃N₂O₃F₂ (MW = 402.44); mass spectroscopy (MH⁺) 402.

Using the above procedure, followed by crystallization from acetonitrile gave a single isomer:

^1H -nmr (DMSO- d_6): δ = 4.46 (m, 1H), 5.03 (d, 1H).

$\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_3\text{F}_2$ (MW = 402.44); mass spectroscopy (MH^+) 402.

5

Example 2-7

Synthesis of

5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-
10 L-alanine (Example B) and 5-amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol hydrochloride (Example 2-A), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $\text{CHCl}_3/\text{MeOH}$.

$\text{C}_{26}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_3$ (MW = 450.48); mass spectroscopy (MH^+) 451.

15 Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_3$; C, 69.32 H, 5.37 N, 6.22. Found: C, 69.02 H, 5.53, N, 6.34.

3: Cyclic Ketone Derivatives

20

GENERAL PROCEDURE 3-A

Jones Oxidation Procedure

The compound to be oxidized was stirred in acetone and the Jones reagent was added in portions until the starting material was consumed. The reaction
25 mixture was quenched with isopropanol and the mixture was filtered through Celite and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic portion was dried over sodium sulfate and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography and/or recrystallization.

30

GENERAL PROCEDURE 3-B

Swern Oxidation Procedure

To a stirred mixture of oxalyl chloride (0.15 mL, 1.2 mmol) in 10 mL of dichloromethane cooled to -78°C was added DMSO (0.106 mL, 1.5 mmol) and the mixture was stirred for 10 minutes. A solution of th alcohol (0.1828 g, 0.60 mmol) in 20 mL of chloroform was added dropwise. The reaction
5 mixture was stirred at -78°C for 2 hours, and then 0.5 mL (3.6 mmol) of triethylamine was added. Stirring was continued for 1 hour and then the mixture was allowed to warm to room temperature and stirring was continued at ambient temperature overnight. The mixture was then diluted with 50 mL of dichloromethane, washed with brine (3x), dried over magnesium sulfate,
10 filtered and evaporated to dryness to give the crude product which as typically purified by column chromatography.

Example 3-1

15

Synthesis of 1-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)- aminoindan-2-one

Following General Procedure 3-A using the product from Example 2A-2, the title compound was prepared as a solid having a melting point of 221-
20 224°C. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 15% methanol/dichloromethane) and purification was by silica gel chromatography using 5% methanol/dichloromethane as the eluant, followed by recrystallization from 1-chlorobutane/acetonitrile.

NMR data was as follows:

25 ^1H -nmr (DMSO- d_6): $\delta = 1.25$ (d, 3H), 4.34 (m, 1H), 5.22 (d, 1H), 8.37 (d, 1H), 8.72 (d, 1H).

$\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{F}_2$ (MW = 372.38); mass spectroscopy (M^+) 372.34.

Example 3-2

30

Synthesis of 2-(N'-(Phenylacetyl)-L-alaninyl)aminocyclohexan-1-one

Following General Procedure 3-B above using 2-(N'-(phenylacetyl)-L-alaninyl)-amino-1-cyclohexanol (Example 2-4), the title compound was prepared as a solid having a melting point of 150-157°C. Purification was by silica gel chromatography using 3% methanol/
5 dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.24-7.40 (m, 5H), 6.7-6.9 (m, 1H), 6.1 (m, 1H), 4.5 (m, 1H), 4.40 (m, 1H), 3.61 (s, 2H), 3.59 (s, 2H), 2.55 (m, 2H), 2.38 (m, 1H), 2.13 (m, 1H), 1.72-1.92 (m, 2H), 1.63 (m, 1H), 1.32 (m, 4H).

10 ¹³C-nmr (CDCl₃) δ = 207.3, 171.75, 171.69, 170.8, 170.6, 134.6, 134.5, 129.3, 129.2, 128.9, 127.3, 127.2, 57.93, 57.88, 48.8, 48.7, 43.5, 40.99, 40.96, 35.0, 34.8, 27.8, 23.96, 23.92, 18.7, 18.4.

C₁₇H₂₇N₃O₃ (MW = 302.38).

15 Example 3-3

Synthesis of

5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one

Using General Procedure 3-A and using 5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol (Example 2-7), the title compound was prepared. The product was purified by flash
20 chromatography using 97:3 CHCl₃/MeOH.

NMR data was as follows:

25 ¹H-nmr (CDCl₃): δ = 7.61-7.16 (m, 8H), 6.78 (m, 2H), 6.69 (m, 1H), 6.31 and 6.21 (two d, 1H), 5.51 (d, 1H), 4.67 (m, 1H), 3.66 (m, 2H), 3.49 (two s, 2H), 1.49 and 1.38 (two m, 3H).

C₂₆H₂₂F₂N₂O₃ (MW = 448.46); mass spectroscopy (MH⁺) 449.

Anal. Calcd for C₂₆H₂₂F₂N₂O₃; C, 69.63 H, 4.94 N, 6.25. Found: C, 69.67 H, 4.85, N, 6.23.

Example 3-4

Synthesis of
1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
aminobenz[f]cycloheptan-2-one

5 Following General Procedure 3-A and using 1-(N'-(3,5-difluorophenyl-
acetyl)-L-alaninyl)-aminobenz[f]cycloheptan-2-ol (Example 2-6), the title
compound was prepared.

4. Lactones

10 Example 4-1

Synthesis of
3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino- γ -butyrolactone

15 Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and α -amino- γ -butyrolactone hydrobromide (Aldrich),
the title compound was prepared as a solid having a melting point of 174-
177°C. The reaction was monitored by tlc on silica gel (R_f = 0.52 in 10%
methanol/dichloromethane) and purification was by silica gel chromatography.

NMR data was as follows:

20 ^1H -nmr (CDCl_3): δ = 8.4 (m, 2H), 7.1 (m, 1H); 7.0 (m, 2H); 4.6 (m, 1H);
4.4 (m, 2H); 3.52 (s, 2H); 2.2 (m, 2H); 1.22 (m, 3H).

^{13}C -nmr (CDCl_3): δ = 175.6, 172.7, 169.2, 112.8, 106.6, 102.2, 65.6,
48.5, 48.3, 41.6, 28.6, 18.7.

$\text{C}_{15}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_4$ (MW = 326); mass spectroscopy (MH^+) 327.

25 Example 4-2

Synthesis of
3-(N'-(3,4-dichlorophenyl)-D,L-alaninyl)amino- γ -butyrolactone

30 Following General Procedure A and using *N*-(3,4-dichlorophenyl)-D,L-
alanine (Example A) and α -amino- γ -butyrolactone hydrobromide (Aldrich), the
title compound was prepared. The reaction was monitored by tlc on silica gel
(R_f = 0.19 in 60% EtOAc/hexane) and purification was by silica gel
chromatography using 60% EtOAc/hexanes as the eluent.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.56 (d, J = 7 Hz, 3H), 2.0-2.15 (m, 1H), 2.75-2.9 (m, 1H), 3.75-3.90 (m, 1H), 4.0 (brs, 1H), 4.2-4.35 (m, 1H), 4.45 (t, J = 7, 1H), 4.5-4.7 (m, 1H), 6.4-6.5 (m, 1H), 6.67 (d, J = 3 Hz, 1H), 7.0-7.1 (m, 1H), 7.2-7.3 (m, 1H).

¹³C-nmr (CDCl₃): δ = 20.0, 30.7, 49.4, 55., 66.5, 113.7, 115.5, 112.8, 131.5, 133.7, 146.3, 174.5, 175.5.

C₁₃H₁₄Cl₂N₂O₃ (MW = 317.17); mass spectroscopy (M⁺) 317.

Example 4-3

Synthesis of 4-(N'-(Cyclopentylacetyl)-L-alaninyl)amino- 1,1-dimethyl-3-isochromanone

Following General Procedure A above using *N*-(cyclopentylacetyl)-L-alanine and 4-amino-1,1-dimethyl-3-isochromanone, the title compound could be prepared.

Example 4-4

Synthesis of 4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1,1-dimethyl-3-isochromanone

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine and 4-amino-1,1-dimethyl-3-isochromanone, the title compound could be prepared.

5. Lactams

GENERAL PROCEDURE 5-A

N-Alkylation of Lactams

To a stirred solution of a BOC-protected α-aminocaprolactam (6.87 g, 30 mmol) in DMF (150 mL) was added in portions 97% NaH (1.08g, 45 mmol). Bubbling occurred immediately and followed by heavy precipitation. After 10 min., benzyl bromide (3.93 mL, 33 mmol) was added. The precipitate dissolved

quickly and in about 10 min. a clear solution was obtained. The reaction mixture was stirred overnight and then evaporated as completely as possible on a rotovap at 30°C. Ethyl acetate (100 mL) was added to the residue and this mixture was washed with water, brine, and dried over magnesium sulfate. After
5 filtration and concentration, a thick liquid (10 g) was obtained which was then chromatographed over silica gel with 1:3 ethyl acetate/hexane as the eluant to provide 5.51 g (58%) of the N-benzylated product as an oil. Other lactams and alkylating agents may be used in this procedure to obtain a wide variety of N-alkylated lactams. Various bases, such as $\text{LiN}(\text{SiMe}_3)_2$, may also be employed.

GENERAL PROCEDURE 5-B

BOC Removal Procedure

The BOC-protected compound in a 1:1-2:1 mixture of CH_2Cl_2 and trifluoroacetic acid was stirred until tlc indicated complete conversion, typically
15 2 hours. The solution was then stripped to dryness and the residue was taken up in ethyl acetate or CH_2Cl_2 . The solution was washed with saturated aqueous NaHCO_3 and the aqueous phase was adjusted to a basic pH, then extracted with ethyl acetate or CH_2Cl_2 . The organic phase was washed with saturated aqueous NaCl and dried over MgSO_4 . The solution was stripped free of solvent on a
20 rotary evaporator to yield the product.

GENERAL PROCEDURE 5-C

Synthesis of α -Aminolactams

The Schmidt reaction was conducted on 4-ethylcyclohexanone using
25 hydroxyamine sulfonic acid as described in Olah, *Org. Synth. Collective*, Vol. VII, page 254, to provide 5-ethylcaprolactam in 76% yield. Using the procedure described in Watthey, et al., *J. Med. Chem.*, 1985, 28, 1511-1516, this lactam was then dichlorinated with PCl_5 at the alpha position and reduced by hydrogenation to provide four isomeric monochlorides (two racemic mixtures).
30 The two racemic mixtures were separated from each other by column chromatography using silica gel and each racemic mixture was reacted with

sodium azide to yield the corresponding azide which was hydrogenated to provide the corresponding α -aminolactams. Other cycloalkanones may be employed in this procedure to provide a wide variety of α -aminolactams. In some cases, such as when preparing the 9-membered ring α -aminolactam, longer reaction times, higher reaction temperatures and an excess of sodium azide may be required. For example, the 9-membered ring α -aminolactam required 5 equivalents of sodium azide, a reaction temperature of 120°C and a reaction time of 4 days. Such conditions can be readily determined by those of ordinary skill in the art.

GENERAL PROCEDURE 5-D

Synthesis of 4-Amino-1,2,3,4-tetrahydroisoquinoline-3-ones

The 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one derivatives employed in this invention can be prepared by the following art-recognized procedures. The conditions for these reactions are further described in D. Ben-Ishai, et al., *Tetrahedron*, 43, 439-450 (1987). The following intermediates were prepared via this procedure:

- 3-amino-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-amino-7-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
- cis* and *trans*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-amino-2-phenethyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 4-amino-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one
- 9-amino(flouren-1-yl)glycine δ -lactam-1,2,3,4-tetrahydroisoquinolin-3-one.

Step A - Preparation of N-Bismethoxycarbonylaminoacetic Acid: To one mole equivalent of glyoxylic acid in 2 liters of ethanol-free chloroform was added two mole equivalents of methyl carbamate and 0.1 mole equivalent of naphthalene sulfonic acid. The reaction mixture was then brought to a reflux for 6 hours. Water was removed using an inverse Dean Stark trap. The reaction was then cooled and the product filtered and washed with chloroform. The

white solid was recrystallized from ethyl acetate/hexanes to give a white powder in 65% yield.

Step B - Coupling Procedure: To 0.0291 moles of N-
5 bismethoxycarbonylaminoacetic acid (or the appropriate carboxylic acid) in 200 mL of THF was added one mole equivalent of EDC•HCl, a benzylamine, HOBT, and diisopropylethylamine. The reaction was allowed to stir at room temperature for 18 hours and then poured into a separatory funnel and extracted into ethyl acetate. The ethyl acetate solution was washed with 1 molar K_2CO_3
10 and then 1 molar HCl. The organic layer was dried over Na_2SO_4 , filtered and solvent removed to give the crystalline benzylamide of N-bismethoxycarbonylaminoacetic acid. This material was used without further purification. Typical yields range from 40 - 55%.

Step C - Cyclization Procedure: The benzylamide of N-
15 bismethoxycarbonylaminoacetic acid (0.008 moles) was dissolved in 75 mL of methanesulfonic acid and allowed to stir over night at room temperature. The reaction mixture was poured over ice and extracted into ethyl acetate. The ethyl acetate extract was washed with 1 molar K_2CO_3 and then 1 N HCl. The organic
20 layer was dried over Na_2SO_4 , filtered and the solvent removed to give the crystalline 4-methoxycarbonylamino-1,2,3,4-tetrahydroisoquinoline-3-one in 50-90% yield. This material was used without further purification.

Step D - Removal of the Methoxyoxycarbonyl Group (MOC): To the 4-
25 methoxycarbonylamino-1,2,3,4-tetrahydroisoquinoline-3-one (3.4 mmoles) in 30 mL of acetonitrile was added 2 mole equivalents of trimethylsilyliodide (TMSI). The reaction mixture was heated to 50-80°C for 3 hrs and then cooled and poured into a separatory funnel. The reaction mixture was diluted with ethyl acetate and washed with 1 molar K_2CO_3 and then with 5% $NaHSO_3$. The
30 organic layer was dried over Na_2SO_4 and filtered. The solvent was removed

under reduced pressure to give the 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one derivative. Typical yields range from 50-87%.

Step E - Alternative Procedure for Removal of the Methoxyoxycarbonyl

5 Group: To 3.8 mmoles of the MOC-protected compound was added 10 mL of 30% HBr in acetic acid and this reaction mixture was heated to 60°C for 3 hrs. The mixture was then cooled and hexanes were added. The hexanes layer was decanted off and the residue as placed under reduced pressure to give a tan solid. This solid was slurried in ether and filtered to give the 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one hydrobromide salt. Typical yields range from 57-10 88%.

Example 5-A

Synthesis of

15 **3-Amino-1,2,3,4-tetrahydroquinolin-2-one**

Step A: Sodium (0.30g, 110M%) was added to anhydrous ethanol (45 mL) and the reaction mixture was stirred until homogenous. Diethyl N-acetylaminomalonate (2.51 g, 100 M%) was added in one portion and this mixture was stirred for 1 h. 2-Nitrobenzyl bromide (2.5g, 100M%) was then20 added in one portion and the reaction mixture was stirred for 3 h. The reaction was poured into water and extracted with ethyl acetate (3x) and then backwashed with water (3x) and brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (30% EtOAc/hexanes) yielded diethyl N-acetylamino-2-nitrobenzylmalonate in 82% yield.

25

Step B: Diethyl N-acetylamino-2-nitrobenzylmalonate (1g, 100M%) was dissolved in a minimum amount of EtOH. Pd/C (10%, 0.05g) was added and the reaction mixture was subjected to 50 psi of H₂ for 3 hours. The reaction was then filtered thru a pad of celite. Additional EtOH (25mL) and TsOH30 (catalytic amount, 0.01g) were added and this mixture was refluxed for 2 hours. The reaction was rotoevaporated to a residue and then partitioned between water and ethyl acetate. The water layer was extracted with ethyl acetate (3x) and the

combined ethyl acetate extracts were washed with water (3x) and then brine (1x). Treatment with MgSO_4 and rotoevaporation yielded pure 3-(N-acetylamino)-3-carboethoxy-1,2,3,4-tetrahydroquinolin-2-one (89% yield).

5 Step C: 3-(N-Acetylamino)-3-carboethoxy-1,2,3,4-tetrahydroquinolin-2-one (0.75 g, 100M%) was suspended in 6N HCl (25 mL) and the mixture was heated to 100°C for 3 hours. The reaction was cooled, rotoevaporated to a residue and then partitioned between water and ethyl acetate. The water was extracted with ethyl acetate (3x) and the combined ethyl acetate extracts were
10 then washed with water (3x) and then brine (1x). Treatment with MgSO_4 followed by rotoevaporation yielded 3-(R,S)-amino-1,2,3,4-tetrahydroquinolin-2-one (72% yield).

Example 5-B

Synthesis of

15 4-Amino-1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of 4-cyanopyridine (Aldrich) (0.150 moles) in 300 mL of dry ether was added 1.1 eq. of phenylmagnesium bromide (Aldrich) dropwise. The reaction was refluxed for 2 hours and then stirred overnight at room temperature. Sodium borohydride (1.0 eq.) was added dropwise as a
20 solution in 200 mL of methanol (CAUTION -- very exothermic). The reaction was then heated to reflux for 6 hours, cooled and quenched with a saturated solution of ammonium chloride. The solution was decanted from the salt in the reaction mixture and acidified with 1N HCl. After washing the aqueous layer with ethyl acetate, the pH of aqueous layer was adjusted to about 9.0 with 1N
25 sodium hydroxide (cold). The aqueous layer was then extracted with ethyl acetate and the organic extracts washed with brine, dried over Na_2SO_4 , filtered and concentrated to give 4-pyridyl- α -benzyl amine as a thick yellow oil.

Step B: Following General Procedure 5-D and using 4-pyridyl- α -benzyl amine, the title compound was prepared.
30

Example 5-C

Synthesis of

4-Amino-1-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: 2-Pyridyl- α -benzyl amine was prepared by substituting 2-cyanopyridine (Aldrich) for 4-cyanopyridine in the procedure described in Example 5-B.

Step B: Following General Procedure 5-D and using 4-pyridyl- α -benzyl amine, the title compound was prepared.

Example 5-D

Synthesis of

4-Amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: Following the procedure described in J. Med. Chem., 1982, 25, 1248, and using 3-benzoyl-pyridine (Aldrich), 3-pyridyl- α -benzyl amine was prepared.

Step B: Following General Procedure 5-D and using 3-pyridyl- α -benzyl amine, the title compound was prepared.

Example 5-E

Synthesis of

4-Amino-7-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a Parr bottle containing 3-benzoylbenzoic acid (0.044 moles) (Aldrich) in 150 mL of ethyl acetate and 4.5 mL of concentrated H_2SO_4 was added 10 grams of 5% Pd/C. The mixture was hydrogenated on a Parr apparatus under hydrogen (45 psi) overnight. The reaction mixture was then filtered through Hyflo, washing with ethyl acetate. The filtrate was dried over Na_2SO_4 , filtered and concentrated to give an oil. The oil was slurried in hexane and the resulting white solid was collected by filtration to afford 3-benzylbenzoic acid, which was used without further purification.

Step B: To the product from Step A (0.0119 moles) was added 150 mL of CH_2Cl_2 , one drop of DMF, 10 mL of oxalyl chloride, and the mixture was stirred at room temperature for 3 hours. After cooling to 10°C , 30 mL of NH_4OH (exothermic) was added and the mixture was stirred for 30 min. The reaction mixture was then concentrated and the resulting residue diluted with ethyl acetate. The organic layer was washed with 1N NaOH, brine, dried over Na_2SO_4 , and concentrated to give the 3-(benzyl)benzamide as a white solid, which was used without further purification.

Step C: To a solution of 3-(benzyl)benzamide (.0094 moles) from Step B in 70 of toluene was added 8 mL of Red-Al® (65+ wt. % solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene, Aldrich) (CAUTION -- reaction very exothermic). The reaction mixture was then heated at 60°C for 2 hours and then poured over ice. The resulting mixture was extracted with ethyl acetate and the combined extracts were washed with water and brine. The organic layer was extracted with 1N HCl and the aqueous layer washed with ethyl acetate. The pH of the aqueous layer was then adjusted to about 9.0 with 1N NaOH and extracted with ethyl acetate. The organic extracts were washed with water and brine and then concentrated to give 3-(benzyl)benzyl amine.

Step D: Following General Procedure 5-D and using 3-(benzyl)benzyl amine, the title compound was prepared.

Example 5-F

Synthesis of 4-Amino-6-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of 4-biphenylcarboxamide (Aldrich) (0.025 mole) in 150 mL of THF cooled to 10°C was added a solution of 1.5 eq of LAH (1M in THF) dropwise. The reaction mixture turned from a white slurry to a green homogenous solution and then to a yellow homogeneous solution. The reaction was then quenched with 2.5 mL of 1N NaOH. The mixture was then filtered through Hyflo and extracted with ethyl acetate. The organic layer was then

washed with 1N HCl. The pH of the resulting aqueous layer was adjusted to about 9 with 1N NaOH and extracted with ethyl acetate. The organic extracts were washed with water and brine, and then dried over Na₂SO₄, filtered and concentrated to give 4-(phenyl)benzyl amine as a white solid.

Step B: Following General Procedure 5-D and using 4-(phenyl)benzyl amine, the title compound was prepared.

Example 5-G

Synthesis of

cis- and *trans*-4-Amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: Following General Procedure 5-D and using α -phenylbenzylamine (Aldrich), 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one was prepared.

Step B: To a solution of 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (0.00158 moles) from Step A in 20 mL of CH₂Cl₂ was added 2.0 eq. of triethylamine and Boc anhydride (1.1 eq.). The reaction was stirred overnight at room temperature and then concentrated. The residue was diluted with ethyl acetate and water. The pH of the aqueous layer was adjusted to 3.0 with sodium bisulfate and the layers were separated. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by LC 2000, eluting with ethyl acetate/hexanes (70:30) to give a white solid containing a 1:1 mixture of *cis*- and *trans*-4-(N-Boc-amino)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one isomers. This mixture was recrystallized from ethyl acetate to give the pure *trans* isomer and a *cis* isomer-enriched mixture of *cis* and *trans* isomers. This mixture was recrystallized again from ethyl acetate/hexanes (70:30) to give the pure *cis* isomer.

Step C: The *cis* isomer and the *trans* isomer from Step B were separately deprotected using General Procedure 8-J to give *cis*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one and *trans*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one.

Example 5-H

Synthesis of

4-Amino-7-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

5 Step A: To a solution of 1-bromo-3-phenylbenzene (Aldrich) (0.0858 moles) in 300 mL of dry THF cooled to -78°C was added tert-butyl lithium (2 eq.) (1.7M in hexane) dropwise. The reaction mixture was stirred for 40 min. at -78°C and then quenched with 2 eq. of DMF (13.24 mL). The resulting mixture was stirred for 20 min. and then poured into a separatory funnel and extracted with CH_2Cl_2 . The organic extracts were washed with water, dried over Na_2SO_4 ,
10 filtered and concentrated to give a brown oil. This oil was purified by LC 2000 chromatography, eluting with ethyl acetate/hexanes (5:95) to give 3-biphenylcarboxaldehyde.

15 Step B: To a solution of 3-biphenylcarboxaldehyde (0.011 eq.) in 30 mL of methanol was added 10 eq. of 7N NH_3/MeOH and NaCNBH_4 (2 eq.). A yellow gum precipitated from solution. The solution was then heated at 60°C until gum dissolved and the solution was stirred at room temperature overnight. The reaction mixture was then concentrated and the resulting residue diluted with ice water and ethyl acetate. The organic layer was then washed with brine and
20 extracted with 5N HCl. The pH of the aqueous layer was then adjusted to 12 and the aqueous layer was extracted with cold ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give 3-(phenyl)benzyl amine as an oil.

25 Step C: Following General Procedure 5-D and using 3-(phenyl)benzyl amine, the title compound was prepared.

Example 5-I

Synthesis of

4-Amino-1-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

30 Step A: To a solution of benzoyl chloride (0.123 moles) (Aldrich) in 600 mL of CH_2Cl_2 was added 2.0 eq. of phenethylamine (Aldrich) dropwise. The

reaction mixture was stirred at room temperature for 3 hours and then poured into a separatory and extracted with CH_2Cl_2 . The organic extracts were washed with water and 1N HCl, and then dried over Na_2SO_4 , filtered and concentrated to give N-phenethyl benzamide.

5

Step B: Reduction of N-phenethyl benzamide using the procedure of Example 5-E, Step C afforded N-benzyl-N-phenethylamine as an oil.

Step C: Following General Procedure 5-D and using N-benzyl-N-phenethylamine, the title compound was prepared.

10

Example 5-J

Synthesis of 3-Amino-1-methyl-2-indolinone Monohydrochloride

Step A: (2,3-Dihydro-1-methyl-2-oxo-1H-indol-3-yl)carbamic acid methyl ester (CAS No. 110599-56-9) was prepared using the procedure described in Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* **1987**, *43*, 439-450. The starting materials for this preparation were N-methylaniline (CAS# 100-61-8, Eastman Kodak Co.), glyoxylic acid (CAS# 298-12-4, Aldrich), and methyl carbamate (CAS# 598-55-0, Aldrich).

15

20

Step B: The product from Step A (333.5 mg) in 31% HBr in AcOH (10 mL) was heated to 50-60°C for 2 hours. The resulting orange solution was concentrated to a thick orange oil which was dissolved in EtOAc (15 mL) and the product extracted into 1 M aq. HCl (10 mL). The aqueous acid was neutralized with aq. NaHCO_3 and the product extracted into CH_2Cl_2 (10 x 10 mL). HCl (gas) was passed through the combined CH_2Cl_2 extracts to form a purple solution. The solution was concentrated to provide the title compound (262.8 mg) as a purple solid.

25

30

Example 5-K

Synthesis of

3-Amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl/Tin Complex

Step A: - Synthesis of 4-Phenyl-3,4-dihydrocarbostyryl

5 4-Phenyl-3,4-dihydrocarbostyryl (CAS# 4888-33-9) was prepared in two steps using the procedure described by Conley, R. T.; Knopka, W. N. *J. Org. Chem.* 1964, 29, 496-497. The starting materials for this preparation were cinnamoyl chloride (Aldrich) and aniline (Aldrich). The title compound was purified by flash chromatography eluting with CH₂Cl₂/EtOAc (4:1).

Step B: - Synthesis of 1-Methyl-4-phenyl-3,4-dihydrocarbostyryl

10 To a suspension of NaH (1.2 eq., 0.537 g of 60% dispersion in mineral oil) in THF (50 mL) under N₂ at 0°C was added the product from Step A (1.0 eq., 2.50 g) in THF (50 mL) via cannula over a period of 5 minutes. The resulting pale yellow mixture was stirred at 0°C for 10 minutes, then MeI (2.0 eq., 1.39 mL) was added. The opaque yellow mixture was allowed to slowly (ice bath not removed) warm to ambient temperature with stirring for 15 hours. 1M Aq. HCl (50 mL) and EtOAc (250 mL) were added and the phases partitioned. The organic phase was washed with dilute NaHCO₃ (1 x 100 mL), brine (1 x 100 mL), then dried over MgSO₄, filtered, concentrated, and the residue purified by flash chromatography eluting with CH₂Cl₂/EtOAc (19:1 gradient to 15:1) to provide 1-methyl-4-phenyl-3,4-dihydrocarbostyryl.

Step C: - Synthesis of 3-Azido-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl

25 Following General Procedure 8-K, 3-azido-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl was prepared as a white solid. The product was purified by flash chromatography eluting with CH₂Cl₂/hexanes/EtOAc 15:15:1.

30 Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.46 (d, 1H, J = 10.57 Hz), 4.18 (d, 1H, J = 10.63 Hz).

Step D: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl/Tin Complex

To a mixture of SnCl_2 (350.7 mg) in MeOH (7 mL) under N_2 at 0°C was added the product from Step C (257.4 mg) in MeOH/THF (5 mL/5 mL) via cannula over a period of 1 minute. The cooling bath was removed the solution allowed to warm to ambient temperature for 8 hours (No starting material by TLC). The solution was concentrated to a yellow foam, THF (10 mL) was added and the mixture was re-concentrated and used without further purification.

Example 5-L

Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl

Step A: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl

3-Amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl was prepared following General Procedure 8-F using 3-azido-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl from Example 5-K, Step C. The product was purified by L.C. 2000 eluting with EtOAc/hexanes (4:1) to yield a white solid.

Selected $^1\text{H-NMR}$ data for the title compound (CDCl_3): $\delta = 4.03$ (d, 1H, $J = 12.8$ Hz), 3.92 (d, 1H, $J = 12.7$ Hz).

Step B: - Synthesis of 3-(4-Chlorobenzylimine)-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl

To a solution of the product from Step A (1 eq., 239.6 mg) in CH_2Cl_2 (10 mL) under N_2 at ambient temperature was added 4-chlorobenzaldehyde (1.05 eq., 140 mg, Aldrich), Et_3N (1.4 eq., 185 mL), and MgSO_4 (3.6 eq., 411 mg). The resultant mixture was stirred at room temperature for 73 hours. The solids were removed by filtration through a plug of Celite, rinsing with CH_2Cl_2 , and the filtrate concentrated to provide 3-(4-chlorobenzylimine)-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl as a thick white foam.

Step C: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl

To a solution of diisopropylamine (1.05 eq., 0.132 mL) in THF (5 mL) under N₂ at -78°C was added a solution of n-BuLi (1.05 eq., 0.588 mL of a 1.6 M solution in hexanes) and the result solution was stirred for 30 minutes. To this solution was added the product from Step B (1.0 eq., 336 mg) in THF (2 mL) via cannula. The solution was allowed to warm to 0°C, then quenched with 1 M aq. HCl (3 mL) and allowed to warm to room temperature with stirring overnight. The product was extracted into H₂O and washed with EtOAc (1 x), then the aqueous acid was basified with 1 M aq. K₂CO₃ and the product extracted into EtOAc. The EtOAc extract was dried over Na₂SO₄, filtered, and concentrated to give 3-amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl.

Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.31 (d, 1H, J = 6.6 Hz).

Example 5-M

Synthesis of

3-Amino-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl/Tin Complex

Step A: - Synthesis of 1-*tert*-Butoxycarbonyl-4-phenyl-3,4-dihydrocarbostyryl

1-*tert*-Butoxycarbonyl-4-phenyl-3,4-dihydrocarbostyryl was prepared from the product of Example 5-K, Step A (CAS# 4888-33-9) by the Boc procedure for aryl amides described by Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chemica Scandinavica B* 1986, 40, 745-750; employing (Boc)₂O (Aldrich) and catalytic DMAP (Aldrich) in acetonitrile. The product was purified by flash chromatography eluting with CH₂Cl₂ gradient to CH₂Cl₂/EtOAc (19:1) and isolated as a pale yellow oil.

Step B - Synthesis of 3-Azido-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl

Following General Procedure 8-K using the product from Step A, the title compound was prepared as a 12.4:1 mixture of *trans/cis* isomers which were separated by flash chromatography eluting with hexanes/Et₂O (6:1 gradient to

4:1) in the first column and hexanes/EtOAc (12:1) in a second column. The pure *trans* isomer was used in Step C.

Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.45 (d, 1H, J = 11.1 Hz), 4.24 (d, 1H, J = 11.2 Hz).

5

Step C: - Synthesis of 3-Amino-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl/Tin Complex

To a mixture of SnCl₂ (450.6 mg) in MeOH (9 mL) under N₂ at 0°C was added the product from Part D (433.0 mg) in MeOH (15 mL) via cannula over a period of 1 minute. The cooling bath was removed the solution allowed to warm to ambient temperature for 17 hours. The solution was concentrated to an amorphous yellow solid and used without further purification.

10

Example 5-N

15

**Synthesis of
(S)-3-Amino-1-benzyl-δ-valerolactam**

Step A: - Synthesis of L-(+)-Ornithine Methyl Ester Hydrochloride

Into a stirred suspension of L-(+)-ornithine hydrochloride (Aldrich) in methanol was bubbled anhydrous hydrochloric acid gas until the solution was saturated. The reaction mixture was capped with a rubber septum and stirring was continued overnight at room temperature. The solvent was then stripped under reduced pressure and the residue triturated with ether. The resulting solid was dried under reduced pressure to afford L-(+)-ornithine methyl ester hydrochloride as a white solid (97% yield).

20

25

Step B: - Synthesis of (S)-3-Amino-δ-valerolactam

Sodium spheres in oil (2.0 eq.) (Aldrich) were washed with hexanes (2x) and methanol (2.3 mL/mmol) was slowly added. The reaction mixture was stirred under nitrogen until the sodium dissolved and then L-(+)-ornithine methyl ester hydrochloride (1 eq.) in methanol (2.3 mL/mmol) was added dropwise. The reaction mixture was stirred for 16 hours and then diluted with diethyl ether (5 mL/mmol) and filtered to remove the solids. The solvent was then removed

30

under reduced pressure and the residue was heated at 70°C for 3 hours under reduced pressure. The residue was then triturated with dichloromethane/ether, the solvent decanted and the resulting residue dried under reduced pressure to afford (S)-3-amino- δ -valerolactam (44% yield).

5

Step C: - **Synthesis of N-Boc-(S)-3-Amino- δ -valerolactam**

(S)-3-Amino- δ -valerolactam (1 eq.) was dissolved in dioxane and the solution was chilled to 0°C. BOC-anhydride (1.3 eq.) was added and the ice bath was removed allowing the solution to come to room temperature and stirring was continued for 16 hours. The solution was rotary evaporated to afford N-Boc-(S)-3-amino- δ -valerolactam.

10

Step D: - **Synthesis of (S)-3-Amino-1-benzyl- δ -valerolactam**

Following General Procedure 5-A and using N-Boc-(S)-3-amino- δ -valerolactam and benzyl bromide provided N-Boc-(S)-3-amino-1-benzyl- δ -valerolactam. Removal of the Boc group using General Procedure 5-B afford the title compound.

15

Example 5-O

20

**Synthesis of
4-Amino-2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane Hydrochloride**

Step A: - **Synthesis of 2-Aza-3-oxobicyclo[3.2.1]octane and 3-Aza-2-oxobicyclo[3.2.1]octane (9:1 Mixture)**

To (\pm)-norcamphor (Aldrich) in 1 mL/mole of acetic acid was added 1.5 eq. of hydroxylamine-O-sulfonic acid. The reaction mixture was heated to reflux under nitrogen for 1 hour and then saturated sodium carbonate and dilute sodium hydroxide were added. The resulting mixture was extracted with dichloromethane and the organic extracts washed with brine, dried over sodium sulfate, and the solvent removed under reduced pressure. Purification of the residue by column chromatography afforded a 9:1 mixture of 2-aza-3-oxobicyclo[3.2.1]octane and 3-aza-2-oxobicyclo[3.2.1]octane.

25

30

Step B: - **Synthesis of 2-Aza-2-benzyl-3-oxobicyclo[3.2.1]octane**

Following General Procedure 5-A and using the product for Step A and benzyl bromide, 2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane was prepared.

5 Step C: - **Synthesis of 2-Aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane**

To a solution of 2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane in THF was added 2.5 eq. of 1M t-BuOK/THF (Aldrich) and the resulting mixture was stirred for 30 minutes. Isoamyl nitrite (1.5 eq.) was then added dropwise and
10 the reaction mixture was stirred overnight. To the reaction mixture was added 3N HCl and this mixture was extracted with ethyl acetate and the organic extracts washed with water, dried, and concentrated under reduced pressure. The residue was triturated with ether/hexanes, the solvents decanted and the residue dried under reduced pressure to afford 2-aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane as a tan liquid (41% yield). This procedure is further
15 described in Y. Kim, *Tetrahedron Lett.* 30(21), 2833-2636 (1989).

Step D: - **Synthesis of 2-Aza-2-benzyl-4-amino-3-oxobicyclo[3.2.1]octane**

20 A solution of 2-aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane in 10 mL/mmol of ethanol and 5.8 mL/mmol of 3N HCl containing 0.5 g/mmol of 10% Pd/C was saturated with hydrogen gas to 45 psi. The mixture was shaken for 3 hours and then filtered through a layer of Celite. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford the title
25 compound as a solid (86% yield). This procedure is further described in E. Reimann, *Arch. Pharm.* 310, 102-109 (1977).

Example 5-1

30 **Synthesis of
3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-
amino-γ-butyrolactam**

Following General Procedure E above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-γ-butyrolactam (prepared by the procedure of

S. Wilkinson, *J. Chem. Soc.* 1951, 104), the title compound was prepared as a solid having a melting point of 217-222°C. The reaction was monitored by tlc on silica gel ($R_f = 0.19$ in 1:9 methanol/dichloromethane).

NMR data was as follows:

5 ^1H -nmr (DMSO- d_6): $\delta = 1.20$ (m, 3H), 1.75 (m, 1H), 2.27 (m, 1H), 3.15 (m, 2H), 3.51 (s, 1H), 3.52 (s, 1H), 4.28 (m, 2H), 6.99 (m, 2H), 7.09 (m, 1H), 7.85 (m, 1H), 8.19 (m, 1H), 8.34 (d, $J = 7.8$ Hz, 1H).

^{13}C -nmr (DMSO- d_6): $\delta = 18.7, 28.4, 28.5, 37.98, 38.00, 41.3, 41.5, 48.07, 48.11, 49.4, 49.5, 101.9$ (t, $J = 25.3$ Hz), 112.2 (m), 140.8, 162.1 (dd, $J = 13.5, 243.6$ Hz), 168.6, 168.7, 172.27, 172.29, 174.2, 174.3.

10 $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3\text{F}_2$ (MW = 325.32); mass spectroscopy (MH^+) 326.

Example 5-2

Synthesis of

15 3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- δ -valerolactam

Following General Procedure A and using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino- δ -valerolactam (prepared by the procedure of D. W. Adamson, *J. Chem. Soc.* 1943, 39), the title compound was prepared.

20

Example 5-3

Synthesis of

1-Benzyl-3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)-amino- δ -valerolactam

25 Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-benzyl- δ -valerolactam (Example 5-N), the title compound was prepared as a solid having a melting point of 172-175°C. The reaction was monitored by tlc on silica gel ($R_f = 0.39$ in 10% methanol/dichloromethane) and purification was by silica gel chromatography.

30 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.5$ (m, 1H); 7.37 (d, $J=7.7$, 1H); 7.3 (m, 5H); 6.80 (d, $J=7.9$, 2H); 6.65 (t, $J=9.1$, 8.9, 1H); 4.7 (m, 2H); 4.6 (m, 1H); 4.3 (m, 1H); 3.50 (s, 2H); 3.2 (m, 2H); 1.9 (m, 4H); 1.3 (m, 3H).

^{13}C -nmr (CDCl_3): $\delta = 173.2, 170.3, 169.8, 165.2, 161.9, 139.4, 137.1, 129.3, 128.4, 113.0, 112.8, 103.4, 102.0, 51.5, 51.3, 49.5, 47.1, 43.2, 27.7, 21.5, 19.4$.

$\text{C}_{23}\text{H}_{25}\text{F}_2\text{N}_3\text{O}_3$ (MW = 429); mass spectroscopy (MH^+) 430.

5

Example 5-4

Synthesis of 3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 4-methyl- ϵ -caprolactam

10 Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-4-methyl- ϵ -caprolactam (General Procedure - C), the title compound was prepared as a mixture of diastereomers. The reaction was monitored by tlc on silica gel ($R_f = 0.18$ in 5% MeOH/dichloromethan).

NMR data was as follows:

15 ^1H -nmr ($\text{DMSO}-d_6$; 2 diastereomers): $\delta = 8.36$ (m, 1H), 7.78 (m, 2H), 7.06 (1H), 6.96 (m, 2H), 4.32 (m, 2H), 3.50 (s, 2H), 3.14 (m, 1H), 3.04 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.08-1.55 (m, 3H), 1.20 (d, $J = 7.1$ Hz, 3H), 0.80 (m, 3H).

20 ^{13}C -nmr ($\text{DMSO}-d_6$; 2 diastereomers): $\delta = 174.1, 174.0, 171.9, 171.8, 169.1, 168.9, 162.4$ (dd, $J = 13.6, 246.0$ Hz), 140.9 (t, $J = 10.1$ Hz), 112.4 (dd, $J = 2.4, 24.2$ Hz) 102.0, (t, $J = 26.0$ Hz), 54.2, 54.0, 48.5 (overlapping), 41.4, 36.7, 36.4, 34.5, 34.3, 28.2, 28.0, 18.9, 18.8, 18.6, 18.0.

$\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3\text{F}_2$ (MW = 367.40); mass spectroscopy ($\text{M}+\text{Na}$) 390.5.

25

Example 5-5

Synthesis of 3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1,2,3,4-tetrahydroquinolin-2-one

30 Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1,2,3,4-tetrahydroquinolin-2-one (Example 5-A), the title compound was prepared as a mixture of diastereomers. The reaction was monitored by tlc on silica gel ($R_f = 0.38$ in 25% ethyl acetate/hexanes) and

purification was by flash chromatography using 25% ethyl acetate/hexanes as the eluant.

NMR data was as follows:

¹H-nmr (DMSO-d₆; 2 diastereomers): δ = 10.34 (d, 1H), 8.41 (d, 1H), 8.23 (t, 1H), 7.20 - 6.86 (m, 7H), 4.40 (m, 2H), 3.52 (s, 2H), 3.52 (s, 2H), 3.05 - 2.79 (m, 2H), 1.29 (d, 1.5H), 1.24 (d, 1.5H).

¹³C-nmr (DMSO-d₆; 2 diastereomers): δ = 172.66, 169.31, 169.21, 169.13, 168.89, 137.85, 128.58, 126.46, 127.94, 122.88, 122.79, 122.69, 122.64, 115.48, 112.97, 112.88, 112.73, 112.59, 112.51, 102.24, 48.61, 48.17, 41.68, 31.72, 18.96, 18.87.

C₂₀H₁₉N₃O₃F₂ (MW = 387.39).

Example 5-6

Synthesis of

1-Benzyl-3-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1,2,3,4-tetrahydroquinolin-2-one

Following General Procedure C above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1-benzyl-1,2,3,4-tetrahydroquinolin-2-one (General Procedure 5-A), the title compound was prepared as a solid having a melting point of 196-199°C. The reaction was monitored by tlc on silica gel (R_f = 0.35 in 5% methanol/dichloromethane) and purification was by flash chromatography using 5% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.4-6.8 (m, 12H), 6.7 (m, 1H), 6.45 (d, 1H), 5.4 (d, 1H), 4.9 (d, 1H), 4.6 (m, 2H), 3.55 (s, 2H), 3.45-3.40 (2xd, 1H), 2.85 (t, 1H), 1.45 (t, 3H).

¹³C-nmr (CDCl₃): δ = 172.7, 172.6, 169.9, 169.7, 169.2, 169.2, 165.4, 165.2, 162.1, 161.9, 139.3, 138.7, 138.6, 136.8, 129.4, 129.3, 128.7, 128.0, 126.9, 124.8, 124.8, 124.6, 124.5, 116.5, 113.1, 113.05, 113.0, 112.9, 112.86, 112.8, 112.8, 112.7, 103.8, 103.5, 103.1, 50.1, 49.7, 49.6, 48.0, 47.9, 43.5, 32.3, 32.12, 32.1, 19.4, 19.2.

C₂₇H₂₅N₃O₃F₂ (MW = 477.51); mass spectroscopy (MH⁺) 478.

Example 5-7

Synthesis of
4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
1,2,3,4-tetrahydroisoquinolin-3-one

5 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-
L-alanine and 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one, the title compound
was prepared as a solid having a melting point of 243-244°C.

NMR data was as follows:

10 ¹H-nmr (DMSO-d₆): δ = 8.46 (bt, J = 8.25 Hz, 2H), 8.36-8.38 (bd, J = 4
Hz, 1H), 7.3-7.0 (m, 7H), 5.34-5.39 (bd, J = 10 Hz, 1H), 4.5-4.4 (m, 2H), 4.2-
4.23 (m, 1H), 3.56 (s, 2H), 1.33 (d, J = 7 Hz, 3H).

C₂₀H₁₉N₃O₃F₂ (MW = 387.1); mass spectroscopy: 387.

Example 5-8

Synthesis of
4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-2-benzyl-
1,2,3,4-tetrahydroisoquinolin-3-one

15 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-
alanine (Example B) and 4-amino-2-benzyl-1,2,3,4-tetrahydroisoquinoline-3-one
20 (General Procedure 5-D), the title compound was prepared as a solid having a
melting point of 144-145°C.

NMR data was as follows:

25 ¹H-nmr (DMSO-d₆): δ = 7.8 (bd, 0.5H), 7.57 (bd, 0.5H), 7.26-7.0 (m, 9H),
6.8-6.6 (m, 2H), 6.66-6.3 (m, 1H), 5.5-5.43 (m, 1H), 4.79-4.45 (m, 5H), 4.10 (t,
J = 14 Hz, 1H), 3.49 (s, 2H), 5.52 (d, J = 7.0 Hz, 1.5H), 1.49 (d, J = 7.0 Hz,
1.5H).

C₂₇H₂₅N₃O₃F₂ (MW = 477); mass spectroscopy: 477.

Example 5-9

Synthesis of
4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-methyl-
1,2,3,4-tetrahydroisoquinolin-3-one

30

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-one (General Procedure 5-D), the title compound was prepared as a solid having a melting point of 205-206°C.

5 NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 8.6-8.24 (m, 3H), 7.3-7.0 (m, 7H aromatic), 5.4-5.39 (m, 1H), 4.58-4.4 (m, 2H), 3.54 (s, 2H), 1.49-1.38 (m, 1H), 1.35-1.3 (m, 6H).

C₂₁H₂₁N₃O₃F₂ (MW = 401); mass spectroscopy: 401.

10

Example 5-10

Synthesis of

4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

15 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (General Procedure 5-D), the title compound was prepared as a solid having a melting point of 200-205°C.

NMR data was as follows:

20 ¹H-nmr (DMSO-d₆): δ = 9.06 (bt, J = 2 Hz, 1H), 8.69-8.43 (m, 2H), 7.55-7.0 (m, 2H), 6.1 (bd, J = 8 Hz, 0.25H), 5.7-5.5 (m, 1H), 5.5 (bd, J = 8 Hz, 0.25H), 5.2-5.19 (bd, J = 8 Hz, 0.5H), 4.48-4.4 (m, 1H), 3.57-3.5 (m, 2H), 3.15 (s, 1H), 1.4-1.2 (m, 3H).

C₂₆H₂₃N₃O₃F₂ (MW = 463); mass spectroscopy: 463.2.

25 By employing the above procedure using *trans*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one and purifying the resulting product by LC 2000 chromatography, eluting with dichloromethane/methanol (97:3), the following isomers of *trans*-4-(*N'*-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one were prepared:

30 Isomer 1: m.p. = 249-250°C.

Isomer 2: m.p. = 232-233°C.

By employing the above procedure using *cis*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one and purifying the resulting product by LC 2000 chromatography, eluting with dichloromethane/methanol (97:3), the following isomers of *cis*-4-(*N'*-(3,5-difluorophenylacetyl)-L-alaninyl)amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one were prepared:

Isomer 1: m.p. = 244.1-244.5°C.

Isomer 2: m.p. = 247-248°C.

Example 5-11

10

Synthesis of 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-6-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-6-fluoro-1,2,3,4-tetrahydroisoquinoline-3-one (General Procedure 5-D), the title compound was prepared as a solid having a melting point of 195-200°C.

NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 8.6-8.41 (m, 3H), 7.4-7.24 (m, 1H), 7.09-6.98 (m, 4H), 6.8-6.77 (bd, J = 9 Hz, 1H), 5.43-5.30 (m, 1H), 4.46-4.42 (m, 2H), 4.23-4.19 (m, 1H), 3.34 (s, 2H), 1.37 - 1.31 (m, 3H).

C₁₉H₁₈N₃O₃F₂ (MW = 405.3); mass spectroscopy: 405.

Example 5-12

25

Synthesis of 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-7-fluoro-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenyl)acetyl-L-alanine (Example B) and 4-amino-7-fluoro-1,2,3,4-tetrahydroisoquinoline-3-one (Example 5-E), the title compound was prepared. The product was purified by slurrying in ether/hexanes (1:1) and by LC 2000 chromatography, eluting with methanol/ethyl acetate (1:99), to give the product as a solid (Isomer 1: m.p. = 230-235°C; Isomer 2: m.p. = 195-200°C).

NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 7.25-6.9 (m, 6H), 5.4 (d, J = 8 Hz, 1H), 4.6-4.4 (m, 2H), 3.55 (s, 2H), 1.35 (d, J = 7.5 Hz, 1.5H), 1.32 (d, J = 7.2 Hz, 1.5H).
C₂₀H₁₈N₃O₃F₃ (MW = 405); mass spectroscopy: 405.

5

Example 5-13

Synthesis of 4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-2-phenethyl- 1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-
alanine (Example B) and 4-amino-2-phenethyl-1,2,3,4-tetrahydroisoquinoline-3-
one (General Procedure 5-D), the title compound was prepared as a solid having
a melting point of 75-76°C.

C₂₇H₂₇N₃O₃F₂ (MW = 491); mass spectroscopy: 491.2.

15

Example 5-14

Synthesis of 4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-2-methyl- 1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and 4-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-
one (General Procedure 5-D), the title compound was prepared as a solid
having a melting point of 174-175°C.

NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 8.57-8.47 (m, 1H), 8.45 (d, J = 7.6 Hz, 1H), 7.26-
7.06 (m, 7H aromatic), 5.38 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 16 Hz, 1H), 4.41
(pentet, J = 8 Hz, 1H), 4.42 (d, J = 16 Hz, 1H), 3.5 (s, 2H), 2.9 (s, 3H), 1.34
(d, J = 8 Hz, 1.5 Hz), 1.32 (d, J = 8 Hz, 1.5H).

C₂₁H₂₁N₃O₃F₂ (MW = 401); mass spectroscopy: 401.

30

Example 5-15

Synthesis of 4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-6-phenyl- 1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-6-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (General Procedure 5-D), the title compound was prepared. The product was purified by LC 2000 chromatography, eluting with ethyl acetate.

5 NMR data was as follows:

¹H-nmr (CD₃OD/CDCl₃): δ = 8.8 (bd, 0.5H), 7.74 (bd, 0.5H), 7.4-7.16 (m, 6H), 6.69 (bs, 1H), 6.69 (bs, 1H), 6.5 (m, 1H), 5.39 (bs, 1H), 4.45-3.95 (m, 4H), 1.37-1.33 (m, 3H).

C₂₆H₂₃N₃O₃F₂ (MW = 463.49); mass spectroscopy: 463.4.

10

Example 5-16

Synthesis of 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-7-phenyl- 1,2,3,4-tetrahydroisoquinolin-3-one

15 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-7-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (Example 5-H), the title compound was prepared as a solid having a melting point > 240°C (dec.).

NMR data was as follows:

20 ¹H-nmr (CDCl₃): δ = 7.5-7.18 (m, 10H), 6.85-6.74 (m, 4H), 4.9-4.57 (m, 1H), 4.56-4.37 (m, 2H), 3.58 (s, 1H), 3.55 (s, 1H), 1.53 (d, J = 6 Hz, 1.5H), 1.47 (d, J = 6 Hz, 1.5H).

C₂₆H₂₃N₃O₃F₂ (MW = 463); mass spectroscopy: 463.

25

Example 5-17

Synthesis of (*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)- (9-aminofluoren-1-yl)glycine δ-Lactam

30 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and (9-aminofluoren-1-yl)glycine δ-lactam (General Procedure 5-D), the title compound was prepared as a solid having a melting point > 240°C (dec.).

NMR data was as follows:

^1H -nmr (DMSO- d_6): δ = 8.0-6.8 (bm, 10H), 6.3-5.75 (bs, 1H), 5.75-5.4 (bs, 1H), 4.1-4.5 (bs, 1H), 3.7-3.35 (bm, 2H), 3.3 (s, 2H), 1.4-1.0 (bm, 3H).

$\text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_3\text{F}_2$ (MW = 461); mass spectroscopy: 461.

5

Example 5-18

Synthesis of

3-(N'-(Phenylacetyl)-L-alaninyl)amino- ϵ -caprolactam

Following General Procedure B above using N-(phenylacetyl)-L-alanine (Example A) and 3-amino- ϵ -caprolactam (Sigma), the title compound was prepared as a solid having a melting point of 200-202°C. The reaction was monitored by tlc on silica gel (R_f = 0.30 in 1:9 methanol/dichloromethane).

10

NMR data was as follows:

^1H -nmr (DMSO- d_6): δ = 8.35 (m, 1H), 7.85 (m, 2H), 7.28-7.32 (m, 5H), 4.22-4.40 (m, 2H), 3.46 (s, 2H), 2.98-3.13 (m, 2H), 1.53-1.90 (m, 4H), 1.26-1.40 (m, 1H), 1.20 (m, 4H).

15

^{13}C -nmr (DMSO- d_6) δ = 174.05, 174.02, 171.2, 171.1, 169.9, 169.8, 136.31, 131.29, 129.1, 129.0, 128.2, 126.3, 51.3, 48.3, 42.0, 40.6, 31.2, 31.0, 28.8, 27.6, 18.2, 18.1.

$\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_3$ (MW = 317.39) ; mass spectroscopy (MH $^+$) 316.

20

Example 5-19

Synthesis of

3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)-amino- ϵ -caprolactam

Following General Procedure B above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino- ϵ -caprolactam (Aldrich), the title compound was prepared as a solid having a melting point >225°C. The reaction was monitored by tlc on silica gel (R_f = 0.36 in 1:9 methanol/dichloromethane).

25

NMR data was as follows:

^1H -nmr (DMSO- d_6): δ = 1.10-1.40 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H), 1.55-1.90 (m, 4H), 3.05 (m, 1H), 3.17 (m, 1H), 3.52 (s, 2H), 4.29 (m, 2H), 6.98 (m, 2H), 7.08 (m, 1H), 7.84 (m, 2H), 8.43 (d, J = 7.3 Hz, 1H).

30

^{13}C -nmr (DMSO- d_6) δ = 18.0, 27.6, 28.8, 31.0, 40.6, 41.3, 48.4, 51.3, 101.9 (t, J = 25.6 Hz), 112.3 (dd, J = 7.5, 16.8 Hz), 140.6, 162.1 (dd, J = 13.2, 243.9 Hz), 168.8, 171.1, 174.0.

$\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_3\text{F}_2$ (MW = 353.37); mass spectroscopy (MH^+) 354.

5

Example 5-20

Synthesis of 3-(S)-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino- 1-benzyl- ϵ -caprolactam

10 Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-benzyl- ϵ -caprolactam (prepared from 3-(S)-amino- ϵ -caprolactam and benzyl bromide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared as a solid having a melting point of 176-178°C. The reaction was monitored by tlc on silica gel (R_f = 0.44 in 10% methanol/dichloromethane) and purification was by precipitation from water.

15

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 1.20 (m, 1H), 1.39 (d, J = 7.0 Hz, 3H), 1.50 (m, 1H), 1.65-2.06 (m, 4H), 3.24 (m, 1H), 3.45 (m, 1H), 3.54 (s, 2H), 4.51 (m, 2H), 4.60 (m, 1H), 4.72 (d, 14.5 Hz, 1H), 6.48 (d, J = 7.1 Hz, 1H), 6.72 (m, 1H), 6.83 (m, 2H), 7.20-7.41 (m, 6H).

20

^{13}C -nmr (CDCl_3): δ = 19.0, 26.9, 27.5, 31.7, 42.8, 48.0, 49.0, 51.5, 52.4, 102.6 (t, J = 25.2 Hz), 112.2 (dd, J = 8.0, 17.0 Hz), 127.6, 128.1, 128.7, 136.7, 138.4, 162.9 (dd, J = 12.8, 247.3 Hz), 169.0, 171.0, 172.5.

25

$\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3\text{F}_2$ (MW = 443.50); mass spectroscopy (MH^+) 444.

Example 5-21

Synthesis of 3-(S)-N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1-(2-Methoxyethyl)- ϵ -caprolactam

30

Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-(2-methoxyethyl)- ϵ -caprolactam (prepared from 3-(S)-amino- ϵ -caprolactam and 2-methoxyethyl bromide using

the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared as a solid having a melting point of 102-106°C. The reaction was monitored by tlc on silica gel ($R_f = 0.08$ in 5% methanol/dichloromethane).

NMR data was as follows:

5 ^1H -nmr (CDCl_3): $\delta = 1.38$ (d, $J = 7.1$ Hz, 3H), 1.48 (m, 2H), 1.82 (m, 2H), 1.96 (m, 2H), 3.35 (s, 3H), 3.38 (m, 1H), 3.47-3.70 (m, 7H), 4.55 (m, 2H), 6.75 (m, 2H), 6.85 (m, 2H), 7.42 (d, $J = 6.0$ Hz, 1H).

^{13}C -nmr (CDCl_3): $\delta = 19.0$, 27.1, 27.6, 31.7, 42.8, 48.7, 49.0, 49.9, 52.4, 58.8, 70.9, 102.6 (t, $J = 25.2$ Hz), 112.2 (dd, $J = 7.8$, 16.9 Hz), 138.4, 10
(164.5, 161.4, 161.2 as multiplet), 169.0, 171.0, 172.4.

$\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_4\text{F}_2$ (MW = 411.45); mass spectroscopy (MH^+) 412.

Example 5-22

Synthesis of

15 3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-ethyl- ϵ -caprolactam

Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-ethyl- ϵ -caprolactam (prepared from 3-(S)-amino- ϵ -caprolactam and ethyl iodide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared as a solid having a melting point of 162-165°C. The reaction was monitored by tlc on silica gel ($R_f = 0.43$ in 10% methanol/dichloromethane).

NMR data was as follows:

25 ^1H -nmr (CDCl_3): $\delta = 1.12$ (t, $J = 7.1$ Hz, 3H), 1.40 (m, 2H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.70-2.00 (m, 4H), 3.24 (m, 1H), 3.50 (m, 3H), 3.53 (s, 2H), 4.50 (m, 2H), 6.70 (m, 2H), 6.83 (m, 2H), 7.39 (d, $J = 6.0$ Hz, 1H).

^{13}C -nmr (CDCl_3): $\delta = 13.1$, 19.1, 27.6, 27.7, 31.7, 42.8, 43.5, 48.1, 49.0, 52.3, 102.6 (t, $J = 25.1$ Hz), 112.2 (dd, $J = 7.9$, 17.0 Hz), 138.3, 138.4, 163.0 (dd, $J = 12.8$, 247.1 Hz), 168.9, 170.9, 171.8.

30 $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3\text{F}_2$ (MW = 381.43); mass spectroscopy (MH^+) 382.

Example 5-23

Synthesis of
3-N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
5-ethyl-ε-caprolactam

5 Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-5-ethyl-ε-caprolactam (General Procedure 5-C), the title compound was prepared as a solid. The reaction was monitored by tlc on silica gel ($R_f = 0.13$ in 5% methanol/dichloromethane).

NMR data was as follows:

10 ^1H -nmr (CDCl_3): $\delta = 0.98$ (t, $J = 7.4$ Hz, 3H), 1.31 (d, $J = 7.0$ Hz, 1.5H), 1.35 (d, $J = 7.1$ Hz, 1.5H), 1.55 (m, 1H), 1.65 (m, 3H), 1.82 (m, 2H), 1.95 (m, 1H), 3.06 (m, 1H), 3.41 (m, 1H), 3.49 (s, 1H), 3.52 (s, 1H), 4.55-4.72 (m, 2H), 6.38 (m, 0.5H), 6.63-6.90 (m, 4.5H), 7.37 (d, $J = 6.0$ Hz, 0.5H), 7.52 (d, $J = 6.2$ Hz, 0.5H).

15 ^{13}C -nmr (CDCl_3): $\delta = 12.07, 12.11, 19.0, 19.2, 24.4, 24.5, 31.9, 32.0, 35.0, 35.3, 35.7, 36.9, 37.0, 42.8, 47.4, 47.6, 48.8, 48.9, 102.7$ (t), 102.6 (t), 122.2 (multiplet of 8), $138.35, 138.41, 138.5, 163.0$ (dd; $J = 12.8, 247.1$ Hz), $168.9, 169.2, 171.1, 171.3, 174.8, 174.9$.

$\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3\text{F}_2$ (MW = 381.43); mass spectroscopy (MH^+) 382.

20

Example 5-24

Synthesis of
3-N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
5-ethyl-ε-caprolactam

25 Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-5-ethyl-ε-caprolactam (General Procedure 5-C), the title compound was prepared as a solid having a melting point of 201-204°C (decom.). The reaction was monitored by tlc on silica gel ($R_f = 0.04$ in 5% methanol/dichloromethane).

30 NMR data was as follows:

^1H -nmr (CD_3OD): $\delta = 0.70$ (t, $J = 7.1$ Hz, 3H), 0.78-1.20 (m, 7H), 1.49 (m, 1H), 1.68 (m, 2H), 3.07 (m, 2H), 3.38 (s, 2H), 4.19 (m, 1H), 4.31 (d, $J = 11.0$ Hz, 1H), 6.61 (m, 1H), 6.72 (m, 2H).

^{13}C -nmr (CD_3OD): δ = 11.47, 11.49, 17.8, 17.9, 31.0, 35.97, 36.03, 38.2, 38.3, 41.6, 42.7 (multiplet of 7), 50.7, 50.8, 52.3, 103.0 (2 triplets of 6), 113.2 (2 dd of 8), 140.9, 141.0, 164.3 (dd, J = 15.5, 258.3 Hz), 172.5 (overlapping of 2), 173.7, 173.9, 176.5, 176.6.

5 $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3\text{F}_2$ (MW = 381.43); mass spectroscopy (MH^+) 382.

Example 5-25

Synthesis of 10 3-(N' -(3,5-Difluorophenylacetyl)-L-alaninyl-amino)- 7-benzyl- ϵ -caprolactam

Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-7-benzyl- ϵ -caprolactam (General Procedure 5-C), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.04 in 5% methanol/dichloromethane).

15 NMR data was as follows:

^1H -nmr (CDCl_3): δ = 1.35 (m, 3H), 1.45 (m, 1H), 1.80 (m, 2H), 2.05 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 2.97 (m, 2H), 3.51 and 3.52 (2 s, 3H), 4.60 (m, 2H), 6.50 - 6.85 (m, 5H), 7.15 (m, 2H), 7.26 (m, 3H), 7.45 (m, 1H).

20 ^{13}C -nmr (CDCl_3): δ = 18.7, 20.0, 21.6, 30.2, 30.4, 30.7, 39.1, 39.3, 42.5, 48.70, 48.74, 53.02, 53.06, 53.89, 53.97, 102.5 (, J = 25.4 Hz), 112.2 (dd, J = 8.3, 17.2 Hz), 126.68, 126.74, 128.67, 128.71, 128.9, 138.0, 138.1, 138.6, 138.7, 138.8, 163.0 (dd, J = 13.0, 249.0 Hz), 169.5, 169.6, 172.0, 174.4, 175.0.

25 $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3\text{F}_2$ (MW = 443.50).

Example 5-26

Synthesis of 30 3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1-benzyl-4,7-methano- ϵ -caprolactam

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-benzyl-4,7-methano- ϵ -caprolactam (i.e., 4-amino-2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane hydrochloride from Example 5-O), the title compound was prepared as an oil. The reaction was monitored by

tlc on silica gel ($R_f = 0.42$ in 10% methanol/dichloromethane) and purification was by silica gel chromatography.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.3$ (m, 5H); 6.82 (t, $J=6.3, 6.0$, 2H); 6.6 (m, 1H);
5 5.14 (dd, $J=6.5, 8.5, 6.4$, 1H); 4.6 (m, 2H); 3.79 (dd, $J=10.3, 4.5, 10.4$,
1H). 3.56 (s, 1H); 3.51 (s, 2H); 2.8 (m, 1H); 2.57 (s, 1H); 1.96 (d, $J=12.1$,
1H); 1.7 (m, 4H); 1.34 (d, $J=7.0$, 3H).

^{13}C -nmr (CDCl_3): $\delta = 173.4, 170.3, 168.9, 165.2, 139.4, 137.3, 129.3,$
128.5, 128.2, 112.9, 112.8, 112.7, 112.6, 103.4, 103.0, 102.7, 59.0, 49.6,
10 43.1, 38.1, 37.8, 36.6, 32.6, 22.7, 19.2.

$\text{C}_{25}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_3$ (MW = 455); mass spectroscopy (MH^+) 456.

Example 5-27.

Synthesis of

15 3-(S)-(N'-(Cyclopentylacetyl)-L-alaninyl)amino- 1-benzyl- ϵ -caprolactam

Following General Procedure A above using *N*-(cyclopentylacetyl)-L-alanine (Example D) and (S)-3-amino-1-benzyl- ϵ -caprolactam (prepared from 3-(S)-amino- ϵ -caprolactam and benzyl bromide using the procedure of Example 6-A
20 and General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel ($R_f = 0.37$ in 5% methanol/dichloromethane) and purification was by preparative thin layer chromatography using 5% methanol/dichloromethane as the eluant.

NMR data was as follows:

25 ^1H -nmr (CDCl_3): $\delta = 7.42$ (d, $J=6.0$ Hz, 1H), 7.15-7.05 (m, 5H), 6.36 (d, 7.2 Hz, 1H), 4.8-4.4 (m, 4H), 3.5-3.3 (m, 1H), 3.3-3.1 (m, 1H), 2.3-1.0 (m, 20H).

^{13}C -nmr (CDCl_3): $\delta = 172.8, 172.4, 171.5, 136.9, 128.7, 128.2, 127.7, 52.3,$
51.4, 48.6, 47.9, 47.6, 42.6, 36.9, 32.34, 32.28, 31.6, 27.5, 26.8, 24.8, 19.0,
30 18.4.

$\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_3$ (MW = 399.54); mass spectroscopy ($\text{M}+\text{Na}$) 422.

Example 5-28

Synthesis of
3-(S)-(N'-(Cyclopentylacetyl)-L-phenylglyciny)amino-
1-benzyl-ε-caprolactam

5 Following General Procedure A above *N*-(cyclopentylacetyl)-L-2-phenylglycine (Example C) and 3-(S)-amino-1-benzyl-ε-caprolactam (prepared from 3-(S)-amino-ε-caprolactam and benzyl bromide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel ($R_f = 0.40$ in 5% methanol/dichloromethane) and purification was by preparative thin layer chromatography using 5% methanol/dichloromethane as the eluant.

10 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.4\text{--}7.15$ (m, 11H), 6.79 (d, $J=6.6$ Hz, 1H), 5.48 (d, $J=7.2$ Hz, 1H), 4.5 (m, 3H), 3.4-3.1 (m, 2H), 2.3-1.0 (m, 17H).

15 ^{13}C -nmr (CDCl_3): $\delta = 172.3, 172.1, 168.9, 138.0, 129.0, 128.6, 128.2, 128.1, 127.6, 127.0, 57.1, 52.6, 51.3, 47.8, 42.5, 36.8, 32.33, 32.27, 31.4, 27.4, 26.8, 24.7$.

$\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_3$ (MW = 461.61); mass spectroscopy ($\text{M}+\text{Na}$) 484.

20 Example 5-29

Synthesis of
3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaniny)amino-
1-(2-phenethyl)-ε-caprolactam

25 Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-(2-phenethyl)-ε-caprolactam (prepared from 3-(S)-amino-ε-caprolactam and 2-phenethyl bromide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel ($R_f = 0.36$ in 5% methanol/dichloromethane) and purification was by preparative thin layer chromatography using 5% methanol/dichloromethane as the eluant.

30 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.60$ (d, $J=6.3$ Hz, 1H), 7.3-7.1 (m, 6H), 6.81 (m, 2H), 6.66 (m, 1H), 4.6 (m, 2H), 3.75 (m, 1H), 3.51 (s, 2H), 3.5-3.4 (m, 2H),

3.05 (m, 1H), 2.8 (m, 2H), 1.95-1.6 (m, 4H), 1.5-1.1 (m (includes d at 1.36, J=7.2 Hz, 3H), 5H).

¹³C-nmr (CDCl₃): δ = 172.3, 171.5, 169.2, 164.6, 164.5, 161.4, 161.2, 139.0, 138.8, 138.7, 138.6, 128.6, 128.5, 126.4, 112.3, 112.2, 112.05, 111.95, 102.7, 102.3, 102.0, 52.2, 50.8, 49.2, 48.9, 42.4, 34.1, 31.5, 27.3, 27.1, 18.8.

C₂₅H₂₉F₂N₃O₃ (MW = 457.52); mass spectroscopy (M+Na) 480.

Example 5-30

Synthesis of

3-(S)-(N'-(Cyclopentylacetyl)-L-phenylglyciny)amino-1-(2-phenethyl)-ε-caprolactam

Following General Procedure A above using *N*-(cyclopentylacetyl)-L-phenylglycine (Example C) and 3-(S)-amino-1-(2-phenethyl)-ε-caprolactam (prepared from 3-(S)-amino-ε-caprolactam and 2-phenethyl bromide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.47 in 5% methanol/dichloromethane) and purification was by preparative thin layer chromatography using 5% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.4-7.1 (m, 11H), 6.88 (d, J=7.2 Hz, 1H), 5.49 (d, J=7.2 Hz, 1H), 4.2 (m, 1H), 3.7-3.6 (m, 1H), 3.5-3.3 (m, 2H), 3.1-3.0 (m, 1H), 2.9-2.7 (m, 2H), 2.3-1.0 (m, 17H).

¹³C-nmr (CDCl₃): δ = 172.2, 171.0, 169.0, 138.6, 138.2, 129.0, 128.7, 128.6, 128.2, 127.0, 126.5, 57.0, 52.6, 50.8, 49.3, 44.4, 42.5, 36.9, 34.2, 32.4, 32.3, 31.4, 27.5, 27.2, 24.8.

C₂₉H₃₇N₃O₃ (MW = 475.64); mass spectroscopy (M+Na) 498.

Example 5-31

Synthesis of

3-(N'-(3,4-Dichlorophenyl)-D,L-alaniny)amino-ε-caprolactam

Following General Procedure A above using *N*-(3,4-dichlorophenyl)-D,L-alanine (Example Q) and 3-(S)-amino-ε-caprolactam (Sigma), the title compound

was prepared as a solid having a melting point of 199°C. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 50% ethyl acetate/hexanes) and purification was by preparative thin layer chromatography using 50% ethyl acetate/hexanes as the eluant.

5 NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 7.2$ (d, 1H); 6.7 (d, 1H); 6.4 (dd, 1H); 4.30 (bs, 1H); 4.1 (m, 2H); 2.9 (m, 2H); 1.7 (m, 6H); 1.3 (t, 3H).

^{13}C -nmr (DMSO- d_6) $\delta = 175$; 171; 146.7; 133; 131; 121; 114.9; 112.6; 52.4; 28.3; 27.5; 19.5; 18.2; 18.1.

10 $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2\text{Cl}_2$ (MW = 344.24); mass spectroscopy (MH^+) 345.

Example 5-32

Synthesis of 15 3-(S)-(N'-(cyclopropylacetyl)-L-phenylglyciny)amino- 1-methyl- ϵ -caprolactam

Following General Procedure A above using *N*-(cyclopropylacetyl)-L-phenylglycine (Example F) and 3-(S)-amino-1-methyl- ϵ -caprolactam (prepared from 3-(S)-amino- ϵ -caprolactam and methyl iodide using the procedure of Example 6-A and General Procedure 6-B), the title compound was prepared as
20 a solid having a melting point $>200^\circ\text{C}$. The reaction was monitored by tlc on silica gel ($R_f = 0.41$ in 10% methanol/dichloromethane) and purification was by recrystallization from ethyl acetate and hexanes.

NMR data was as follows:

25 ^1H -nmr (CDCl_3): $\delta = 7.5$ -7.2 (m, 7H), 5.49 (d, $J = 6.6$ Hz, 1H), 4.46 (m, 1H), 3.50 (m, 1H), 3.10 (m, 1H), 2.97 (s, 3H), 2.1-1.7 (m, 4H), 1.5-1.3 (m, 2H), 1.0 (m, 1H), 0.6 (m, 2H), 0.2 (m, 2H).

^{13}C -nmr (CDCl_3): $\delta = 172.1$, 171.8, 168.9, 138.1, 129.0, 128.3, 127.0, 57.0, 52.4, 50.2, 41.1, 35.8, 31.3, 27.5, 26.4, 6.8, 4.4.

$\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3$ (MW = 357.46).

Example 5-33

Synthesis of
3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
8-octanelactam

5 Following General Procedure B above using *N*-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and 3-amino-8-octanelactam (i.e., 2-oxo-1-
azacyclononane prepared as described in General Procedure 5-C), the title
compound was prepared as a solid having a melting point of >220°C.

NMR data was as follows:

10 ¹H-nmr (DMSO-d₆): δ = 1.00 - 1.85 (m, 12H), 2.73 (m, 1H), 3.33 (br s,
2H), 3.49 (br s, 2H), 4.07 (m, 1H), 4.28 (m, 1H), 6.95 (m, 2H), 7.06 (m,
1H), 7.75 - 7.90 (m, 2H), 8.30 (d, J = 7.2 Hz, 1H).

15 ¹³C-nmr (DMSO-d₆): δ = 18.2, 18.6, 21.1, 23.5, 27.9, 28.1, 32.3, 32.6,
41.3, 48.0, 48.1, 52.9, 53.0, 102.0 (t, J = 25.9 Hz), 112.4 (d, J = 24.1 Hz),
141.0 (t, J = 11.2 Hz), 162.3)dd, J = 13.5, 244.5 Hz), 168.9, 171.9, 173.1,
173.2.

$C_{19}H_{25}N_3O_3F_2$ (MW = 381.43); mass spectroscopy (M-H) 380.

Example 5-34

20 Synthesis of
4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-7-benzyl-
1,2,3,4-tetrahydroisoquinolin-3-one

25 Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-
alanine (Example B) and 4-amino-7-benzyl-1,2,3,4-tetrahydroisoquinoline-3-one
(General Procedure 5-D), the title compound was prepared as a solid having a
melting point of 159-166°C.

$C_{27}H_{25}N_3O_3F_2$ (MW = 477); mass spectroscopy: 477.

Example 5-35

30 Synthesis of
4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-
1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-benzyl-1,2,3,4-tetrahydroisoquinoline-3-one (Example 5-I), the title compound was prepared as a solid having a melting point of 106-107°C.

5 $C_{27}H_{25}N_3O_3F_2$ (MW = 477.52); mass spectroscopy: 478.

Example 5-36

Synthesis of
10 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (General Procedure 5-D), the title compound was prepared as a solid having a melting point of 115°C.

15 $C_{27}H_{24}N_3O_3F_2$ (MW = 476); mass spectroscopy: 477.

Example 5-37

Synthesis of
20 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-one (Example 5-C), the title compound was prepared as a solid having a melting point of 100°C.

25 $C_{25}H_{22}N_4O_3F_2$ (MW = 464); mass spectroscopy: 464.1.

Example 5-38

Synthesis of
30 4-(*N'*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinoline-

3-one (Example 5-D), the title compound was prepared as a solid having a melting point of 100-120°C.

$C_{25}H_{22}N_4O_3F_2$ (MW = 464); mass spectroscopy: 464.

5

Example 5-39

Synthesis of 4-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 4-amino-1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinoline-3-one (Example 5-B), the title compound was prepared as a solid having a melting point of 100°C.

$C_{25}H_{22}N_4O_3F_2$ (MW = 464); mass spectroscopy: 464.

15

Example 5-40

Synthesis of 3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]- amino-1-methyl-2-indolinone

Following General Procedure I above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1-methyl-2-indolinone monohydrochloride (Example 5-J), the title compound, as a ~ 1:1 diastereomeric mixture at C3 of the indolinone, was prepared as a white solid having a decomposition point of 215-220°C. Purification was by flash chromatography eluting with 3:1 CH_2Cl_2 /EtOAc gradient to straight EtOAc followed by recrystallization from $CHCl_3$. R_f = 0.16 and 0.22 (EtOAc).

25

$C_{20}H_{19}F_2N_3O_3$ (MW 387.39); mass spectroscopy (MH+) 387.0.

Anal. Calcd for $C_{20}H_{19}F_2N_3O_3$: C, 62.01; H, 4.94; N, 10.85. Found: C, 61.76; H, 5.17; N, 10.65.

30

Example 5-41

Synthesis of 3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino- 1-methyl-4-phenyl-3,4-trans-dihydrocarbostyryl

Following General Procedure I above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and the tin complex of 3-amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl (Example 5-K), the title compound, as a ~1:1.8 diastereomeric mixture of the two 3,4-*trans*-dihydrocarbostyryl isomers, was prepared as a white solid (melting point = 118-128 °C). Purification was by flash chromatography eluting with straight EtOAc. $R_f = 0.37$ (EtOAc).

$C_{27}H_{25}F_2N_3O_3$ (MW 477.52); mass spectroscopy (MH+) 477.

Anal. Calcd for $C_{27}H_{25}F_2N_3O_3$: C, 67.91; H, 5.28; N, 8.80. Found: C, 67.78; H, 5.35; N, 8.55.

Example 5-42

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl (Example 5-L), the title compound was prepared as a white solid (m.p. 152-153°C).

$C_{27}H_{25}F_2N_3O_3$ (MW 477.52); mass spectroscopy (MH+) 478.2, (MH-) 476.2.

Anal. Calcd for $C_{27}H_{25}F_2N_3O_3$: C, 67.91; H, 5.28; N, 8.80. Found: C, 67.61; H, 5.41; N, 8.78.

Example 5-43

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-4-phenyl-3,4-*trans*-dihydrocarbostyryl

Step A: Following General Procedure I above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and the tin complex of 3-amino-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl (Example 5-M), 3-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl was prepared.

Step B: The title compound was prepared following General Procedure 5-B using the product from Step A, as a ~1:1.4 diastereomeric mixture of the two 3,4-*trans*-dihydrocarbostyryl isomers. The product was purified by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 94:6) and a second flash chromatography eluting with straight EtOAc to yield a white solid (melting point = 137-147 °C). R_f = 0.42 (EtOAc).

C₂₆H₂₃F₂N₃O₃ (MW 463.49); mass spectroscopy (M+) 463.1

Anal. Calcd for C₂₆H₂₃F₂N₃O₃: C, 67.38; H, 5.00; N, 9.07. Found: C, 67.12; H, 5.06; N, 8.88.

6. Benzazepinone Derivatives and Related Compounds

GENERAL PROCEDURE 6-A

Alkylation of 1-Amino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Step A: 1-Ethoxycarbonylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one was prepared according to the procedure of Ben-Ishai et al., *Tetrahedron*, 1987, 43, 430.

Step B: 1-Ethoxycarbonylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (2.0 g, 100 M%) was dissolved in DMF (30 mL) and NaH (95%, 0.17 g, 100M%) was added in one portion. The reaction mixture was stirred for 1 hour and then the appropriate alkyl iodide (300M%) was added and the mixture was stirred for 12 hours. The reaction was poured into water and extracted with ethyl acetate (3x). The ethyl acetate extracts were then washed with water (3x) and brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (30% EtOAc/hexanes) yielded 1-ethoxycarbonylamino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one in 87% yield.

Step C: 1-Ethoxycarbonylamino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (1.0g, 100M%) was suspended in 30 mL of 30% HBr/HOAc

and heated to 100°C. The reaction mixture was stirred for 5 hours at this temperature and then the reaction was cooled and rotoevaporated to yield 1-amino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one as the hydrobromide salt (100% yield).

5

GENERAL PROCEDURE 6-B

Alkylation of

3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Step A: 3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from α -tetralone using the methods described in Armstrong et al. *Tetrahedron Letters*, 1994, 35, 3239. The following compounds were as prepared by this procedure for use in the following steps:

10

5-methyl-3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (from 4-methyl- α -tetralone (Aldrich)); and

15

5,5-dimethyl-3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (from 4,4-dimethyl- α -tetralone (Aldrich)).

20

Step B: 3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (4.43 g, 100M%) was suspended in t-butanol (30mL) and BOC-anhydride (7.5 mL, 130M%) was added dropwise. The reaction was stirred for 2 hours and then it was rotoevaporated to a residue which was chromatographed with 60% ethyl acetate/hexanes to yield BOC-protected 3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 87% yield.

25

Step C: BOC-protected 3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.5 g, 100M%) was dissolved in DMF (20mL) and NaH (95%, 0.13g, 100M%) was added in one portion. The reaction mixture was stirred for 1 hour and then the appropriate alkyl iodide (300M%) was added and stirring was continued for 12 hours. The reaction was poured into water and extracted with ethyl acetate (3x). The ethyl acetate extracts were washed with water (3x) and then brine (1x). Treatment with MgSO_4 , rotoevaporation, and chromatography

30

(30% EtOAc/hexanes) yielded a BOC-protected 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 80% yield.

5 Step D: The BOC-protected 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.0g, 100M%) was suspended in 30 mL of 1:1 CH₂Cl₂/trifluoroacetic acid and the mixture was stirred for 4 hours. The reaction was then rotoevaporated to yield the 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100% yield).

10 Example 6-A

 Synthesis of

 3-Amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

15 Step A: 3-Amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from 4-methyl- α -tetralone using the methods described in Armstrong et al. *Tetrahedron Letters*, 1994, 35, 3239.

20 Step B: 3-Amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9.3g 100M%) was dissolved in dioxane (300mL) and the solution was chilled to 0°C. BOC-anhydride (13.89g 130M%) was added and the ice bath was removed allowing the solution to come to room temperature and stirring was continued for 16 hours. The solution was rotary evaporated to remove dioxane to provide an off white solid. This solid was recrystallized from CHCl₃ to yield BOC-protected 3-amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 55% yield.

25 Step C: BOC-protected 3-amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100 M%) was dissolved in DMF (20mL) and NaH (95%, 100 M%) was added in one portion and the reaction mixture was stirred for 1 hour. Methyl iodide (300 M%) was added and this mixture was stirred for 12
30 hours. The reaction was then poured into water and extracted with ethyl acetate (3x) then backwashed with water (3x) and then brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (5% MeOH/CH₂Cl₂)

yielded BOC-protected 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 75% yield.

Step D: BOC-protected 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100 M%) was suspended in 30 mL of 1:1 CH₂Cl₂/trifluoroacetic acid. The reaction mixture was stirred for 4 hours. The reaction was then rotoevaporated to yield 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100% yield).

Example 6-B

Synthesis of
5-(L-Alaninyl)-amino-3,3,7-trimethyl-
5,7-dihydro-6H-benz[b]azepin-6-one Hydrochloride

Following the procedure of Example 7-I and using 5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one hydrochloride (Example 6-C), the title compound was prepared.

Example 6-C

Synthesis of 5-Amino-3,3,7-trimethyl-5,7-dihydro- 6H-benz[b]azepin-6-one Hydrochloride

Step A: Following General Procedure 5-A and using N-t-Boc-5-amino-3,3-dimethyl-5,7-dihydro-6H-benz[b]azepin-6-one (General Procedure 6-B, following by Boc protection) and methyl iodide, N-t-Boc-5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one was prepared.

Step B: Following General Procedure 8-N and using N-t-Boc-5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one, the title compound was prepared.

Example 6-D

Synthesis of

3-(S)-Amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

5 Step A: 3-(S)-Amino-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from N-Boc-serine (Bachem) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* 1995, 5(12) 1281-1286.

10 Step B: Following General Procedure 5-A and using the product from Step A, the title compound was prepared.

Example 6-E

Synthesis of

3-(S)-Amino-1-ethyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

15 Step A: 3-(S)-Amino-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from N-Boc-serine (Bachem) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* 1995, 5(12) 1281-1286.

20 Step B: Following General Procedure 5-A and using the product from Step A, the title compound was prepared.

25

Example 6-F

Synthesis of

3-(S)-Amino-1-methyl-5-thia-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

30 The title compound was prepared from N-Boc-cystine (Novabio) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* 1995, 5(12) 1281-1286, followed by General Procedure 5-A.

Example 6-1

Synthesis of

1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

5 Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and 1-amino-3-methyl-1,3,4,5-tetrahydro-2H-3-
benzazepin-2-one, the title compound was prepared. The reaction was
monitored by tlc on silica gel ($R_f = 0.15$ in ethyl acetate) and purification was
by flash chromatography using ethyl acetate as the eluant.

10 NMR data was as follows:

^1H -nmr (CDCl_3 ; 2 diastereomers): $\delta = 8.10$ (m, 1H), 7.58 (d, 0.5H), 7.42 (d, 0.5H), 7.05 (m, 4H), 6.65 (m, 3H), 6.29 (m, 1H), 4.80 (t, 1H), 4.20 (m, 1H), 3.36 (s, 0.5H), 3.34 (s, 0.5H), 3.26 (bd, 2H), 3.10 (m, 2H), 3.01 (s, 3H), 2.98 (s, 3H), 1.36 (d, 3H), 1.29 (s, 3H).

15 ^{13}C -nmr (CDCl_3 ; 2 diastereomers): $\delta = 168.2, 167.9, 165.3, 165.2, 165.1, 164.9, 160.3, 160.1, 157.0, 156.8, 134.4, 134.3, 130.1, 129.9, 129.0, 128.8, 126.0, 123.3, 122.5, 119.5, 119.1, 107.9, 107.8, 107.6, 98.3, 98.0, 97.6, 47.6, 47.4, 44.6, 44.5, 43.7, 43.6, 38.0, 37.8, 30.6, 30.5, 26.6, 14.6, 14.1$.

$\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_3\text{F}_2$ (MW = 415.44); mass spectroscopy (M^+) 415.

Example 6-2

Synthesis of

1-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
3-ethyl-7-fluoro-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

25 Following General Procedure C above using *N*-(3,5-difluorophenylacetyl)-L-
alanine (Example B) and 1-(S)-amino-3-ethyl-7-fluoro-1,3,4,5-tetrahydro-2H-3-
benzazepin-2-one (General Procedure 6-A), the title compound was prepared.
Purification was by flash chromatography using 5% methanol/dichloromethane
as the eluant.

30 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.8-7.7$ (2xd, $J = 7$ Hz, 1H), 7.1-7.0 (m, 2H), 6.8 (m, %H), 6.2 (t, 1H), 4.7 (t, 1H), 4.2 (m, 1H), 3.6-3.4 (m, 6H), 3.2 (m, 2H), 1.5-1.3 (2xd, $J = 7$ Hz, 3H), 1.1 (2xt, $J = 7$ Hz, 3H).

¹³C-nmr (CDCl₃): δ = 177.3, 172.5, 172.1, 169.6, 169.4, 163.8, 160.5, 126.3, 126.2, 125.9, 125.8, 117.4, 117.2, 117.1, 116.9, 113.7, 113.4, 112.4, 112.3, 112.1, 112.0, 103.0, 102.9, 102.7, 102.6, 102.2, 53.3, 51.7, 51.4, 49.2, 49.0, 44.8, 44.5, 42.6, 42.5, 42.4, 42.3, 32.2, 19.0, 13.0, 12.9.

5 C₂₃H₂₄N₃O₃F₃ (MW = 447.19); mass spectroscopy (MH⁺) N/A.

Example 6-4

Synthesis of

3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

10

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.15 in 12% methanol/dichloromethane) and purification was by flash chromatography using 12% methanol/dichloromethane as the eluant.

15

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 9.87 (s, 1H), 8.28 (d, 1H), 8.11 (d, 1H), 7.30 - 6.96 (m, 7H), 4.23 (m, 1H), 4.18 (m, 1H), 3.49 (s, 2H), 2.68 (m, 2H), 2.24 (m, 1H), 1.97 (m, 1H), 1.15 (s, 3H).

20

¹³C-nmr (CDCl₃): δ = 171.95, 171.54, 189.00, 160.74, 141.06, 138.01, 133.91, 129.90, 127.84, 125.58, 122.41, 112.79, 112.46, 102.23, 49.06, 48.47, 41.67, 35.50, 28.39, 18.99.

C₂₁H₂₁N₃O₃F₂ (MW = 401.42); mass spectroscopy (MH⁺) 402.

25

Example 6-5

Synthesis of

3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-benzyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

30

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1-benzyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. Purification was by flash chromatography.

NMR data was as follows:

¹H-nmr (CDCl₃; 2 diastereomers): δ = 7.20 (m, 9H), 6.73 (m, 3H), 5.26 (dd, 1H), 4.76 (dd, 1H), 4.53 (p, 1H), 4.44 (m, 1H), 3.44 (s, 1H), 2.40 (m, 3H), 1.83 (m, 1H), 1.28 (dd, 3H).

¹³C-nmr (CDCl₃; 2 diastereomers): δ = 172.2, 172.1, 171.2, 171.1, 170.0, 169.8, 1565.2, 165.0, 162.0, 140.7, 139.2, 137.4, 136.6, 129.9, 129.1, 128.9, 128.7, 128.5, 128.1, 127.6, 124.0, 112.9, 112.8, 112.7, 112.6, 103.4, 103.1, 102.8, 52.6, 52.5, 50.3, 49.5, 49.4, 43.1, 36.6, 36.5, 28.7, 28.6, 19.4, 19.2.

C₂₈H₂₇N₃O₃F₂ (MW = 491.54); mass spectroscopy (MH⁺) 491.

Example 6-7

Synthesis of

3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure A above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.21 in 3% methanol/dichloromethane) and purification was by flash chromatography using 3% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.20 (m, 4H), 6.86 (d, 1H), 6.68 (m, 3H), 6.33 (d, 1H), 4.40 (m, 3H), 3.46 (s, 2H), 3.36 (s, 3H), 2.78 (m, 1H), 2.57 (m, 2H), 1.84 (m, 1H), 1.29 (d, 3H).

¹³C-nmr (CDCl₃): δ = 171.5, 171.0, 169.4, 165.3, 165.1, 162.0, 161.8, 141.9, 138.7, 135.1, 129.9, 128.6, 127.5, 123.4, 113.0, 112.5, 103.6, 103.3, 103.0, 50.4, 49.5, 43.5, 36.7, 36.1, 28.8, 19.5.

C₂₂H₂₃N₃O₃F₂ (MW = 415.44); mass spectroscopy (M⁺) 415.

Example 6-8

Synthesis of

3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure C above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (prepared from 4-methyltetralone (Aldrich) using General Procedure 6-A), the title compound was prepared as a solid having a melting point of 115-119°C. Purification was by flash chromatography using 5% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.2-7.0 (m, 5H), 6.8-6.5 (m, 4H), 4.5 (m, J = 7 Hz, 1H), 4.3 (m, J = 4 Hz, 1H), 3.5 (s, 2H), 3.35 (s, 3H), 3.05 (m, J = 6.5 Hz, 1H), 2.2 (m, J = 4.5 Hz, 1H), 1.95 (m, 1H), 1.3 (2xd, J = 7 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 172.3, 166.4, 165.9, 164.4, 164.3, 160.0, 159.9, 156.6, 139.9, 136.4, 133.6, 133.2, 122.8, 122.4, 120.5, 118.1, 107.6, 107.3, 98.2, 97.9, 97.5, 95.5, 45.0, 44.9, 44.0, 43.9, 39.8, 39.7, 37.9, 30.7, 30.7, 26.0, 14.0, 13.8, 12.4.

C₂₃H₂₅N₃O₃F₂ (MW = 429.47); mass spectroscopy (MH⁺) 430.

Example 6-9

Synthesis of 3-(3,5-Difluorophenylacetyl)amino- 1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure C above using *N*-(3,5-difluorophenyl)acetic acid (Oakwood) and 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Example 6-A), the title compound was prepared as a solid having a melting point of 185-187°C. Purification was by flash chromatography using 5% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.4-7.1 (m, 4H), 6.9-6.6 (m, 4H), 4.3 (m, J = 8 Hz, 1H), 3.5 (s, 2H), 3.35 (s, 3H), 3.05 (m, J = 6.5 Hz, 1H), 2.3 (m, J = 8 Hz, 1H), 1.95 (m, J = 7 Hz, 1H), 1.3 (d, J = 7.1 Hz, 3H).

¹³C-nmr (CDCl₃): δ = 166.1, 163.8, 160.0, 159.8, 156.7, 156.5, 136.4, 133.8, 133.7, 133.3, 122.8, 122.5, 120.5, 118.1, 107.6, 107.5, 107.3, 107.2, 98.2, 97.8, 97.5, 45.1, 39.9, 38.0, 30.6, 26.0, 12.5.

$C_{20}H_{20}N_2O_2F_2$ (MW = 358.39); mass spectroscopy (MH^+) 359.

Example 6-10

Synthesis of

3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Example 6-D), the title compound was prepared as a solid having a melting point of 110-114°C. The reaction was monitored by tlc on silica gel (R_f = 0.38 in 10% methanol/dichloromethane) and purification was by silica gel chromatography.

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.25 (d, J =4.2, 1H); 7.2 (m, 4H); 6.79 (d, J =5.7, 2H), 6.70 (t, J =2.1, 2.1, 1H); 6.61 (d, J =7.5, 1H); 4.83 (dq, J =7.2, 11.1, 7.5, 1H); 4.55 (dt, J =7.8, 9.3, 5.1, 2H); 4.11 (dd, J =9.9, 11.1, 1H); 3.48 (s, 2H); 3.39 (s, 3H); 1.30 (d, J =6.6, 3H).

^{13}C -nmr ($CDCl_3$): δ = 167.3, 164.4, 160.0, 156.7, 145.2, 133.5, 131.2, 122.9, 120.9, 118.5, 118.1, 107.6, 107.4, 98.3, 37.9, 37.6, 44.5, 44.0, 37.8, 36.6, 14.0.

$C_{21}H_{21}F_2N_3O_4$ (MW = 417); mass spectroscopy (MH^+) 418.

Example 6-11

Synthesis of

3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure A above using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-ethyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Example 6-E), the title compound was prepared as a solid having a melting point of 188-191°C. The reaction was monitored by tlc on silica gel (R_f = 0.43 in 10% methanol/dichloromethane) and purification was by recrystallization from ether/hexanes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.2 (m, 4H); 7.1 (m, 1H); 6.79 (dd, J=6.0, 6.6, 2H); 6.71 (t, J=2.2, 2.2, 1H); 6.43 (dd, J=7.2, 8.8, 1H); 4.8 (m, 1H); 4.6 (m, 2H); 4.2 (m, 2H); 3.50 (s, 2H); 1.31 (d, J=7.1, 3H); 1.16 (t, J=7.1, 3H).

5 ¹³C-nmr (CDCl₃): δ = 172.9, 167.5, 164.8, 164.3, 146.6, 130.2, 123.6, 121.4, 119.3, 118.5, 108.0, 107.7, 98.4, 44.9, 44.4, 39.0, 38.3, 14.3.

C₂₂H₂₃F₂N₃O₄ (MW = 431); mass spectroscopy (MH⁺) 432.

Example 6-12

10 Synthesis of 3-(S)-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino- 1-methyl-5-thia-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure A above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-(S)-amino-1-methyl-5-thia-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Example 6-F), the title compound was prepared as a solid
15 having a melting point of 156-159°C. The reaction was monitored by tlc on silica gel (R_f = 0.17 in 10% methanol/dichloromethane) and purification was by silica gel chromatography.

NMR data was as follows:

20 ¹H-nmr (CDCl₃): δ = 7.63 (d, J=6.05, 1H); 7.43 (t, J=7.7, 7.7, 1H); 7.2 (m, 3H); 6.79 (d, J=6.05, 2H); 6.54 (t, J=7.1, 7.1, 1H); 6.35 (d, J=7.7, 1H); 4.5 (m, 2H); 3.7 (m, 1H); 2.79 (t, J=11.0, 11.5, 1H); 1.29 (d, J=6.6, 3H).

25 ¹³C-nmr (CDCl₃): δ = 172.9, 166.8, 165.8, 164.7, 141.4, 133.8, 131.4, 126.2, 123.4, 122.7, 120.2, 108.0, 107.7, 98.4, 45.3, 44.5, 40.1, 38.3, 33.8, 32.0, 14.3.

C₂₁H₂₁F₂N₃O₃S (MW = 433); mass spectroscopy (MH⁺) 434.

Example 6-13

30 Synthesis of 5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}-amino- 3,3-dimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-3,3-dimethyl-5,7-dihydro-6H-benz[b]azepin-6-one, the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.1$, 5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 6% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (d^6 -DMSO): $\delta = 3.50$ (d, 2H); 9.55 (d, 1H).

MW = 429.47; mass spectroscopy (M^+) 429.

Example 6-14

Synthesis of

5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one hydrochloride (Example 6-C), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.4$, 5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 5% MeOH/ CHCl_3) and crystallization from acetonitrile.

NMR data was as follows:

^1H -nmr (d^6 -DMSO): $\delta = 3.48$ (d, 2H); 4.25 (m, 2H).

MW = 443.50; mass spectroscopy (M^+) 443.

Example 6-15

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one hydrochloride (Example 6-B), the title compound was prepared. The product was purified by chromatography (silica, 3% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.35$ (d, 3H); 5.07 (d, 1H).

MW = 459.49; mass spectroscopy (MH⁺) 460.

Example 6-16

Synthesis of

1-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood) and 1-(N'-(3,5-difluorophenylacetyl)-L-alaninyl)amino-5-phenyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, the title compound was prepared.

Purification was by LC 2000 chromatography using ethyl acetate as the eluant.

C₂₇H₂₅N₃O₃F₂ (MW = 477); mass spectroscopy (MH⁺) 478.1.

Anal. Calc. for C₂₇H₂₅N₃O₃F₂: C, 67.91; H, 5.28; N, 8.8. Found: C, 68.2; H, 5.35; N, 8.58.

Example 6-17

Synthesis of

3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Following General Procedure C above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc (R_f = 0.23, 30% EtOAc/hexanes) and the product was purified by flash chromatography using EtOAc/hexanes as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.1-7.4 (m, 6H), 6.70 (m, 2H), 6.62 (t, 1H), 4.46 (m, 1H), 4.39 (m, 1H), 3.64 (m, 1H), 3.57 (d, 2H), 2.52 (m, 1H), 1.90 (m, 1H), 1.30 (m, 12H).

¹³C-nmr (CDCl₃): δ = 167.3, 167.2, 165.7, 165.0, 164.9, 160.2, 160.1, 156.9, 156.8, 136.4, 136.3, 134.5, 134.4, 123.4, 122.5, 122.0, 119.7, 107.9, 107.8, 107.6, 97.9, 97.8, 45.5, 44.9, 44.9, 44.37, 44.34, 40.0, 39.9, 37.9, 30.6, 36.7, 24.4, 14.2, 14.1, 9.15, 9.12.

C₂₄H₂₉N₃O₃F₂ (MW = 457.52); mass spectroscopy (MH⁺) N/A.

Example 6-18

Synthesis of
3-(3,5-Difluorophenylacetyl)amino-
1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

5 Following General Procedure C above using *N*-(3,5-difluorophenyl)acetic acid (Oakwood) and 3-amino-1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.28$, 25% EtOAc/hexanes) and the product was purified by flash chromatography using EtOAc/hexanes as the
10 eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.38$ (d, 1H), 7.20 (m, 4H), 6.81 (d, 2H), 4.42 (m, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.29 (s, 2H), 2.45 (m, 1H), 1.38 (s, 3H), 1.30 (t, 3H), 1.24 (s, 3H).

15 ^{13}C -nmr (CDCl_3): $\delta = 166.2, 164.2, 160.3, 160.1, 157.0, 156.8, 136.5, 136.3, 134.3, 123.4, 122.6, 122.1, 119.8, 107.9, 107.8, 107.7, 107.6, 98.4, 98.0, 97.7, 45.7, 44.9, 40.0, 38.2, 36.6, 26.8, 24.5, 9.2$.

$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{F}_2$ (MW = 386.45).

20 Example 6-19

Synthesis of
3-(*N'*-(Cyclopentylacetyl)amino-
1-ethyl-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

25 Following General Procedure C above using *N*-(cyclopentylacetyl)-L-alanine (Example D) and 3-amino-1-ethyl-5,5-trimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (General Procedure 6-B), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.25$, 30% EtOAc/hexanes) and the product was purified by flash chromatography using EtOAc/hexanes as the
30 eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.38$ (d, 1H), 7.20 (m, 1H), 6.42 (t, 1H), 4.43 (m, 1H), 3.93 (m, 1H), 3.83 (m, 1H), 2.42 (m, 1H), 2.19 (s, 2H), 1.68 (m, 2H), 1.50 (m, 2H), 1.35 (s, 3H), 1.22 (t, 3H), 1.21 (s, 3H), 1.05 (m, 2H).

¹³C-nmr (CDCl₃): δ = 168.1, 168.0, 167.16, 167.11, 165.7, 136.5, 136.4, 123.3, 122.52, 122.50, 122.14, 122.1, 119.8, 119.7, 55.8, 45.6, 45.5, 44.8, 44.7, 44.08, 44.05, 40.07, 40.01, 38.1, 32.5, 30.67, 30.65, 27.9, 27.8, 26.8, 24.5, 20.3, 14.37, 14.32, 9.58, 9.2, 9.1.

5 C₂₄H₃₅N₃O₃ (MW = 413.56); mass spectroscopy (MH⁺) N/A.

7. Dibenzazepinone Derivatives and Related Compounds

GENERAL PROCEDURE 7-A

10

Preparation of
5-Amino-7-alkyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Derivatives

Step A: Following General Procedure 5-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one and an alkyl halide, the 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

15

Step B: The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) was dissolved in THF and isoamyl nitrite (1.2 eq.) was added. The mixture was cooled to 0°C in an ice bath. NaHMDS (1.1 eq., 1M in THF) was added dropwise. After stirring for 1 hour or until the reaction was complete, the mixture was concentrated then acidified with 1N HCl and extracted with EtOAc. The organic portion was dried and concentrated to yield a crude product which was purified by silica gel chromatography.

20

Step C: The resulting oxime was dissolved in EtOH/NH₃ (20:1) and hydrogenated in a bomb using Raney nickel and hydrogen (500 psi) at 100°C for 10 hours. The resulting mixture was filtered and concentrated to provide an oil which was purified by silica gel chromatography to yield the title compound.

25

30

GENERAL PROCEDURE 7-B

Preparation of
Fluoro-substituted 5,7-dihydro-6H-
dibenz[b,d]azepin-6-one Derivatives

A modification of the procedure of Robin D. Clark and Jahangir, *Tetrahedron*, Vol. 49, No. 7, pp. 1351-1356, 1993 was used. Specifically, an appropriately substituted N-t-Boc-2-amino-2'-methylbiphenyl was dissolved in THF and cooled to -78°C. s-Butyl lithium (1.3M in cyclohexane, 2.2 eq.) was added slowly so that the temperature remained below -65°C. The resulting mixture was allowed to warm to -25°C and was stirred at that temperature for 1 hour. The mixture was cooled to -78°C. Dry CO₂ was bubbled through the mixture for 30 seconds. The mixture was allowed to warm to ambient temperature then was carefully quenched with water. The mixture was concentrated under reduced pressure then was adjusted to pH 3 with 1N HCl. The mixture was extracted with EtOAc and the organic portion was dried and concentrated to yield a crude material. The crude material was dissolved in methanol and the solution was saturated with HCl. The mixture was heated at reflux for 12 hours then was allowed to cool. The mixture was concentrated to provide crude lactam which was purified by chromatography or crystallization.

GENERAL PROCEDURE 7-C

Resolution of 5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

In a round bottom flask was added the racemic freebase amine (1.0 eq.) in methanol followed by di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.). The mixture was concentrated *in vacuo* to a residue and redissolved in a moderate volume of methanol and allowed to stir at room temperature open to the atmosphere (8-72 hours). The solid was removed by filtration. The enantiomeric excess was determined by chiral HPLC (Chiracel ODR) using 15% acetonitrile and 85% H₂O with 0.1% trifluoroacetic acid and a flow rate of 1.0 mL/min at 35°C. The resolved di-*p*-toluoyl-D-tartaric salt was then dissolved in EtOAc and saturated NaHCO₃ until pH 9-10 was reached. The layers were separated and the organic layer was washed again with saturated NaHCO₃, H₂O, and brine. The organic layer was dried over MgSO₄ and the drying agent was removed by filtration. The filtrate was concentrated *in vacuo*. The free amine was dissolved in MeOH and HCl (12M, 1.0 eq.) was added.

The salt was concentrated *in vacuo* and the resulting film was triturated with EtOAc. The HCl salt was filtered and rinsed with EtOAc. The ee was determined by chiral HPLC.

Example 7-A

Synthesis of
5-Amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A - Synthesis of 7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A round bottom flask was charged with sodium hydride (0.295 g, 7.46 mmol) in 9.0 ml of DMF and treated with 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.3 g, 6.22 mmol) (CAS # 20011-90-9, prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein). After stirring at 60°C for 1 h, the solution was treated with methyl iodide (1.16 ml, 18.6 mmol) and stirring continued for 17 h with the exclusion of light. After cooling, the reaction was diluted with CH₂Cl₂/H₂O, washed with NaHSO₄ solution, H₂O, and dried over Na₂SO₄. Evaporation and flash chromatography (SiO₂, CHCl₃) gave 0.885 g (63%) of the title compound as a colorless solid.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.62 (d, 2H), 7.26-7.47 (m, 6H), 3.51 (m, 2H), 3.32 (s, 3H).

C₁₅H₁₃NO (MW = 223.27); mass spectroscopy (MH⁺) 223.

Anal. Calcd for C₁₅H₁₃NO; C, 80.69 H, 5.87 N, 6.27. Found: C, 80.11 H, 5.95 N, 6.23.

Step B - Synthesis of 7-Methyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The compound isolated above (0.700 g, 3.14 mmol) was dissolved in 20 ml of toluene and treated with butyl nitrite (0.733 ml, 6.28 mmol). The reaction temperature was lowered to 0°C and the solution was treated with KHMDS

(9.42 ml, 0.5 M) under N₂ atmosphere. After stirring for 1 h the reaction was quenched with a saturated solution of NaHSO₄, diluted with CH₂Cl₂ and separated. The organic layer was dried over Na₂SO₄ and the title compound purified by chromatography (SiO₂, 98:2 CHCl₃/MeOH) giving 0.59 g (80 %) as a colorless solid.

C₁₅H₁₂N₂O₂ (MW = 252.275); mass spectroscopy (MH⁺) 252.

Anal. Calcd for C₁₅H₁₂N₂O₂; C, 71.42 H, 4.79 N, 11.10. Found: C, 71.24 H, 4.69 N, 10.87.

10 Step C - Synthesis of 5-Amino-7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The oxime isolated above (0.99 g, 3.92 mmol) was hydrogenated in a Parr apparatus at 35 psi over 10 % Pd/C (0.46 g) in 3A ethanol. After 32 h the reaction mixture was filtered through a plug of celite, the filtrate evaporated to a foam and treated with a saturated solution of HCl (g) in Et₂O. The resulting colorless solid was filtered, rinsed with cold Et₂O and vacuum dried to give 0.66 g (61 %) of the title compound.

NMR data was as follows:

¹H-nmr (DMSOd6): δ = 9.11 (bs, 3H), 7.78-7.41(m, 8H), 4.83 (s, 1H), 3.25 (s, 3H).

C₁₅H₁₄N₂O · HCl (MW = 274.753); mass spectroscopy (MH⁺ free base) 238.

Anal. Calcd for C₁₅H₁₄N₂O · HCl; C, 65.57 H, 5.50 N, 10.19. Found: C, 65.27 H, 5.67 N, 10.13.

25

Example 7-B

Synthesis of
(S)- and (R)-5-(L-Alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

30 Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Boc-L-Alanine (0.429 g, 2.26 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.305 g, 2.26 mmol), and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.45 g, 1.89 mmol) (Example 7-A). The

temperature was lowered to 0°C and the reaction mixture treated with EDC (0.449 g, 2.26 mmol) (Alrich) and stirred 17 hours under N₂. The reaction mixture was evaporated, the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The diastereomers were
5 separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 ml/minute.

Isomer 1: Retention time 3.37 minutes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.62-7.33 (m, 9H), 5.26 (d, 1H), 5.08 (m, 1H), 4.34 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.40 (d, 3H).

10 Optical Rotation: $[\alpha]_{20} = -96$ @ 589 nm (c = 1, MeOH).

C₂₃H₂₇N₃O₄ (MW = 409.489); mass spectroscopy (MH⁺) 409.

Anal. Calcd for C₂₃H₂₇N₃O₄; C, 67.46 H, 6.64 N, 10.26. Found: C, 68.42 H, 7.02 N, 9.81.

Isomer 2: Retention time 6.08 minutes.

15 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.74 (bd, 1H), 7.62-7.32 (m, 8H), 5.28 (d, 1H), 4.99 (m, 1H), 4.36 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.46 (d, 3H).

Optical Rotation: $[\alpha]_{20} = 69$ @ 589 nm (c = 1, MeOH).

C₂₃H₂₇N₃O₄ (MW = 409.489); mass spectroscopy (MH⁺) 409.

20 Anal. Calcd for C₂₃H₂₇N₃O₄; C, 67.46 H, 6.64 N, 10.26. Found: C, 67.40 H, 6.62 N, 10.02

Step B - Synthesis of (S)- and (R)-5-(L-Alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

25 The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

30 C₁₈H₁₉N₃O₂.HCl (MW = 345.832); mass spectroscopy (MH⁺ free base) 309.

Optical Rotation: $[\alpha]_{20} = -55$ @ 589 nm (c = 1, MeOH).

Isomer 2:

$C_{18}H_{19}N_3O_2 \cdot HCl$ (MW = 345.832); mass spectroscopy (MH+ free base) 309.
Optical Rotation: $[\alpha]_{20} = 80 @ 589 \text{ nm}$ ($c = 1$, MeOH).

Example 7-C

5

Synthesis of (S)- and (R)-5-(L-Valinyl)-amino-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Valinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10 Boc-L-Valine (0.656 g, 3.02 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), Dipea (1.05 ml, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol)(Example 7-A). The temperature was lowered to 0°C and the reaction mixture treated with EDC (0.601 g, 3.02 mmol)(Alrich) and stirred
15 17 hours under N_2 . The reaction mixture was evaporated, the residue diluted with EtOAc/ H_2O , washed 1.0 N HCl, sat. $NaHCO_3$, brine and dried over Na_2SO_4 . The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 ml/minute.

Isomer 1: Retention time 3.23 minutes.

20 Optical Rotation: $[\alpha]_{20} = -120 @ 589 \text{ nm}$ ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH+) 438

Isomer 2: Retention time 6.64 minutes.

Optical Rotation: $[\alpha]_{20} = 50 @ 589 \text{ nm}$ ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH+) 438

25

Step B - Synthesis of (S)- and (R)-5-(L-Valinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17 hours, the title
30 compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH+ free base) 338.

Optical Rotation: $[\alpha]_{20} = -38$ @ 589 nm ($c = 1$, MeOH).

Isomer 2:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH⁺ free base) 338.

Optical Rotation: $[\alpha]_{20} = 97$ @ 589 nm ($c = 1$, MeOH).

5

Example 7-D

Synthesis of

(S)- and (R)-5-(L-tert-Leucine)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10 Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-tert-LeucinyI)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Boc-L-tert-Leucine (0.698 g, 3.02 mmol) (Fluka) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), Dipea (1.05 ml, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride
15 (0.75 g, 2.75 mmol)(Example 7-A). The temperature was lowered to 0°C and the reaction mixture treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred 17 hours under N₂. The reaction mixture was evaporated, the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The diastereomers were separated on a Chiralcel OD column using
20 10% IPA/heptane at 1.5 ml/minute.

Isomer 1: Retention time 3.28minutes.

Optical Rotation: $[\alpha]_{20} = -128$ @ 589 nm ($c = 1$, MeOH).

$C_{26}H_{33}N_3O_4$ (MW = 451.571); mass spectroscopy (MH⁺) 452

25 Isomer 2: Retention time 5.52 minutes.

Optical Rotation: $[\alpha]_{20} = 26$ @ 589 nm ($c = 1$, MeOH).

$C_{26}H_{33}N_3O_4$ (MW = 451.571); mass spectroscopy (MH⁺) 452

30 Step B - Synthesis of (S)- and (R)-5-(L-tert-LeucinyI)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17 hours, the title

compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{21}H_{25}N_3O_2 \cdot HCl$ (MW = 387.91); mass spectroscopy (MH⁺ free base) 352.

5 Optical Rotation: $[\alpha]_{20} = -34$ @ 589 nm (c = 1, MeOH).

Isomer 2:

$C_{21}H_{25}N_3O_2 \cdot HCl$ (MW = 387.91); mass spectroscopy (MH⁺ free base) 352.

10 Optical Rotation: $[\alpha]_{20} = 108$ @ 589 nm (c = 1, MeOH).

Example 7-E

Synthesis of

5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

Step A - Synthesis of 5-Iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15 A solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 g, 4.77 mmol) (Example 7-A) and Et₃N (2.66 ml, 19.12 mmol) were stirred for 5.0 minutes at -15°C in CH₂Cl₂ and treated with TMSI (1.36 ml, 9.54 mmol). After stirring for 15 minutes I₂ (1.81 g, 7.16 mmol) was added in a single portion and the reaction allowed to warm to 5-10°C over 3 h. The reaction was quenched with
20 sat. Na₂SO₃, diluted with CH₂Cl₂ and separated. The organics were washed with Na₂SO₃ and NaHSO₃ and dried over MgSO₄. After filtration, the organics were concentrated to approximately 20 ml and diluted with an additional 20 ml of hexanes. The title compound was isolated as a tan precipitate by filtration.

25 Step B - Synthesis of 5-Azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The iodide isolate above was dissolved in DMF and treated with 1.2 equivalents of NaN₃. After stirring 17 h at 23°C the mixture was diluted with EtOAc/H₂O, separated, washed with brine and dried over MgSO₄. The title
30 compound was triturated from hot EtOAc as a tan powder.

Step C - Synthesis of 5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

The azide was dissolved in THF/H₂O and stirred at 23°C for 17 h in the presence of 3.0 equivalents of Ph₃P. The reaction was diluted with 50 % HOAc/toluene, separated, the aqueous layer extracted with toluene and evaporated to an oily residue. This was taken to pH 7.0 by the addition of 1 N NaOH, the resulting HOAc salt was collected and vacuum dried. Finally, the compound was treated with Boc anhydride (1.05 equivalents) and Et₃N (2.1 equivalents) in THF. After stirring for 5 h at 23°C the reaction was filtered and the title compound isolated as a colorless powder.

Example 7-F

Synthesis of
5-Amino-7-(2-methylpropyl)-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A - Synthesis of 5-(N-Boc-Amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2g, 0.617 mmol) (Example 7-E) in DMF was treated with Cs₂CO₃ (0.22 g, 0.678 mmol) and warmed to 60°C. To the reaction mixture was added 1-iodo-2-methylpropane (0.078 ml, 0.678 mmol) and stirring continued for 17 h. After cooling to 23 °C the mixture was diluted with CH₂Cl₂, washed with several portions of brine and dried over Na₂SO₄. The title compound was purified by chromatography (SiO₂, CHCl₃/MeOH 9:1).

C₂₃H₂₈N₂O₃ (MW = 380.41); mass spectroscopy (MH⁺) 381

Anal. Calcd for C₂₃H₂₈N₂O₃; C, 72.61 H, 7.42 N, 7.36. Found: C, 72.31 H, 7.64 N, 7.17.

Step B - Synthesis of 5-Amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a slightly colored solid after evaporation and vacuum drying.

Example 7-G

Synthesis of 5-Amino-7-(methoxyacetyl)-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Hydrochloride

5 Step A- Synthesis of 5-(N-Boc-Amino)-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.03, 3.08 mmol) (Example 7-E) in DMF was treated with Cs_2CO_3 (1.10 g, 3.39 mmol) and warmed to 60°C. To the reaction mixture was added bromomethyl acetate (0.321 ml, 3.39 mmol) (Aldrich) and stirring continued for 17 h. After cooling to 23 °C the mixture was diluted with CH_2Cl_2 , washed with several portions of brine and dried over Na_2SO_4 . The title compound was purified by chromatography (SiO_2 , CHCl_3).

$C_{22}H_{24}N_2O_5$ (MW = 396.44); mass spectroscopy (MH⁺) 397

15 Anal. Calcd for $C_{22}H_{24}N_2O_5$; C, 66.65 H, 6.10 N, 7.07. Found: C, 66.28 H, 5.72 N, 6.50.

Step B - Synthesis of 5-Amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

20 The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a colorless solid after evaporation and vacuum drying.

$C_{17}H_{16}N_2O_3 \cdot HCl$ (MW = 332.78); mass spectroscopy (MH+ free base) 297.

25 Example 7-H

Synthesis of
5-Amino-7-(3,3-dimethyl-2-butanonyl)-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

30 Step A- Synthesis of 5-(N-Boc-Amino)-7-(3,3-dimethyl-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2 g, 0.617 mmol) (Example 7-E) in DMF was treated with Cs_2CO_3 (0.3 g, 0.925 mmol) and warmed to 60°C. To the reaction mixture was added 1-chloro-3,3-dimethyl-2-butanone (0.096 ml, 0.74 mmol) (Aldrich) and stirring continued for

17 h. After cooling to 23 °C, the mixture was diluted with CH₂Cl₂, washed with several portions of brine and dried over Na₂SO₄. The title compound was isolated as a colorless solid.

C₂₅H₃₀N₂O₄ (MW = 422.522); mass spectroscopy (MH⁺) 423

5

Step B - Synthesis of 5-Amino-7-(3,3-dimethyl-2-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a colorless solid after evaporation and vacuum drying.

10

Example 7-I

**Synthesis of
L-Alaninyl-5-amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

15

Step A: Following General Procedure D and using N-t-Boc-L-alanine and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, N-t-Boc-L-alaninyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

20

Step B: Following General Procedure 8-N and using the N-t-Boc-L-alaninyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared. Other substituted N-t-Boc-L-alaninyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones can also be prepared by this procedure.

25

Example 7-J

**Synthesis of
L-Valinyl-5-amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

30

Step A: Following General Procedure D and using N-t-Boc-L-valine and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

Step B: Following General Procedure 8-N and using the N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared. Other substituted N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones can also be prepared by this procedure.

5

Example 7-K

Synthesis of

5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-chloro-4-phenylbutane (Aldrich), the title compound was prepared.

10

Example 7-L

Synthesis of

5-Amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and (bromomethyl)cyclopropane (Aldrich), the title compound was prepared.

15

20

Example 7-M

Synthesis of

5-Amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-bromo-2,2,2-trifluoroethane (Aldrich), the title compound was prepared.

25

30

Example 7-N

Synthesis of
5-Amino-7-cyclohexyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one

5 Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and bromocyclohexane (Aldrich), the title compound was prepared.

10

Example 7-O

Synthesis of
5-(L-Alaninyl)amino-9-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

15 Step 1: 2-Bromo-5-fluorotoluene was stirred in THF at -78C. s-BuLi (1.05 eq., 1.3 M in cyclohexane) was slowly added and the mixture was stirred for 45 minutes. Trimethylborate (1.5 eq) was added and the mixture was allowed to warm to ambient temperature. After stirring for 1 hour, pinacol (2 eq.) was added. The mixture was stirred for 16 hours then was concentrated under reduced pressure. The resulting residue was slurried in CH₂Cl₂ and filtered
20 through Celite. The filtrate was concentrated to yield an oil which was purified by chromatography on deactivated silica gel (Et₃N) to yield the arylboronate ester.

25 Step 2: 2-Bromoaniline (1 eq.) and di-t-butyl-dicarbonate (1.1 eq.) were stirred at 80°C for 20 hours. The resulting mixture was allowed to cool and was directly distilled using house vacuum to provide N-t-Boc-2-bromoaniline.

30 Step 3: N-t-Boc-2-bromoaniline (Step 2, 1 eq.), the arylboronate ester (Step 1, 1.1 eq.), K₂CO₃ (1.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.02 eq) were stirred in 20% water/dioxane under nitrogen. The solution was heated at reflux for 10 hours. The mixture was allowed to cool then was concentrated. The resulting residue was partitioned between water and chloroform. The

organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography using 1:1 CH₂Cl₂/hexanes.

5 Step 4: Following General Procedure 7-B and using the substituted biphenyl from step 3, the 9-fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

10 Step 5: 9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq., Step 4), cesium carbonate (1.1 eq., Aldrich) and methyl iodide (1.1 eq., Aldrich) were stirred in dry DMF at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure to provide a residue which was partitioned between EtOAc and water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography to 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one.

15

Step 6: Following General Procedure 7-A, Step B and 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one from Step 5, 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

20 Step 7: Following the procedure of Example 7-I and using 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one from Step 6, the title compound was prepared.

Example 7-P

25

Synthesis of 5-(L-Alaninyl)amino-13-fluoro-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

 Following the procedure of Example 7-O and using 2-bromo-4-fluoroaniline (Step 2, Lancaster) and o-tolylboronic acid (Step 3, Aldrich), the title compound
30 was prepared.

Example 7-Q

Synthesis of
**5-(L-Alaninyl)amino-10-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Following the procedure of Example 7-O and using 2-bromo-4-fluorotoluene (Step 1), the title compound was prepared.

Example 7-R

Synthesis of
10 **5-(L-Alanyl)-amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

 Following the procedure of Example 7-I and using 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-L), the title compound was prepared.

15

Example 7-S

Synthesis of
 **5-(L-Alaninyl)amino-7-phenbutyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20 Following the procedure of Example 7-I and using 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-K), the title compound was prepared.

Example 7-T

Synthesis of
25 **5-(L-Valinyl)amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

 Following the procedure of Example 7-J and using 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-L), the title compound was prepared.

30

Example 7-U

Synthesis of
35 **5-(L-Valinyl)amino-7-phenbutyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-J and using 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-U), the title compound was prepared.

5

Example 7-V

**Synthesis of
5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

10 Step A: Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-bromohexane (Aldrich), 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

15 Step B: Following the procedure of Example 7-J and using 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared.

Example 7-W

20 **Synthesis of
5-(L-Valinyl)amino-10-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-J and using 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-Q), the title compound was prepared.

25

Example 7-X

**Synthesis of
5-(L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

30 Following the procedure of Example 7-J and using the 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-P), the title compound was prepared.

Example 7-Y

Synthesis of
5-(L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

5 Following the procedure of Example 7-J and using the 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-O), the title compound was prepared.

Example 7-Z

10 Synthesis of
(5-Amino-7-methyl-1,2,3,4,5,7-hexahydro-
6H-dicyclohexyl[b,d]azepin-6-one

 The 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-A) was dissolved in a 1:1 mixture of EtOAc/HOAc.
15 5% Rh/C was added and the mixture was stirred at 60°C under 60 psi of hydrogen. After 3 days, the mixture was filtered and the filtrate was concentrated to provide an oil which was purified by SCX-cation exchange chromatography to yield the title compound.

20 Example 7-AA

 Synthesis of
5-(S)-Amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride

 Following General Procedure 7-C using racemic 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 eq.) and di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.) in methanol, the title compound was prepared as a solid.
25 The product was collected by filtration. Enantiomeric excess was determined by chiral HPLC.

 Desired enantiomer 1: retention time of 9.97 minutes.

30 Undesired enantiomer 2: retention time of 8.62 minutes.

 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 9.39 (s, 2H), 7.75-7.42 (m, 8H), 4.80 (s, 1H), 3.30 (s, 3H).

$C_{15}H_{15}ClN_2O$ (MW = 274.75); mass spectroscopy (MH^+) 239.1.

Anal Calcd for $C_{15}H_{15}ClN_2O_3$; C, 65.57; H, 5.50; N, 10.20; Found: C, 65.51, H, 5.61; N, 10.01.

5

Example 7-1

Synthesis of 5-(S)-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino- 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-
10 alanine (Example B) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-A), the title compound was prepared as a colorless solid. The diastereomers were purified by HPLC (Bulk OD-25) using 15% EtOH in heptane as eluent and a flow rate of 1.5 ml/min.

Isomer 1: retention time of 11.4 minutes.

15

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.62-7.33 (m, 8H), 6.79 (m, 2H), 6.71 (m, 1H), 6.47 (m, 1H), 5.24 (d 1H), 4.70 (m, 1H), 3.48 (s, 2H), 3.34 (s, 3H), 1.42 (d, 3H).

Optical Rotation: $[\alpha]_{20} = -125$ @ 589 nm ($c = 1$, MeOH).

$C_{26}H_{23}F_2N_3O_3$ (MW = 463.49); mass spectroscopy (MH^+) 463.

20

Anal. Calcd for $C_{26}H_{23}F_2N_3O_3$; C, 67.38 H, 5.00 N, 9.06. Found: C, 67.49 H, 5.06 N, 8.93.

Example 7-2

Synthesis of 25 5-(S)-[N'-((S)-3,5-Difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one and 5-(S)-[N'-((R)-3,5-Difluorophenyl- α -hydroxyacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

30

Following General Procedure D above using 3,5-difluoromandelic acid and 5-(S)-[L-alaninyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-B), the title compound was prepared as a colorless solid. The diastereomers were purified by flash chromatography using 98:2 $CHCl_3$ /MeOH.

Isomer 1:

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.67 (d, 1H), 7.60-7.28 (m, 8H), 7.15 (d, 1H), 6.98 (m, 2H), 6.74 (m, 1H), 5.21 (d, 1H), 4.94 (d, 1H), 4.61 (m, 1H), 4.56 (m, 1H),
5 3.34 (s, 3H), 1.42 (d, 3H).

Optical Rotation: [α]₂₀ = - 121 @ 589 nm (c = 1, MeOH).

C₂₆H₂₃F₂N₃O₄ (MW = 479.488); mass spectroscopy (MH⁺) 479.

Anal. Calcd for C₂₆H₂₃F₂N₃O₄; C, 65.13 H, 4.83 N, 8.76. Found: C, 65.42 H, 4.73 N, 8.65.

10 Isomer 2:

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.78 (d, 1H), 7.66 (d, 1H), 7.54-7.28 (m, 8H), 6.89 (m, 2H), 6.71 (m, 2H), 5.22 (d, 1H), 4.92 (m, 1H), 4.65 (m, 1H), 4.01 (m, 1H),
15 3.37 (s, 3H), 1.39 (d, 3H).

Optical Rotation: [α]₂₀ = - 146 589 nm (c = 1, MeOH).

C₂₆H₂₃F₂N₃O₄ (MW = 479.488); mass spectroscopy (MH⁺) 479.

Anal. Calcd for C₂₆H₂₃F₂N₃O₄; C, 65.13 H, 4.83 N, 8.76. Found: C, 65.18, 4.82, 8.65.

20

Example 7-3

Synthesis of

5-(S)-[N'-(3,5-Difluorophenyl-α-ketoacetyl)-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following the Jones oxidation procedure (Fieser and Fieser, Reagents for
25 Organic Synthesis, Vol. 1, p. 142) using 5-(S)-[((S/R)-3,5-difluorophenyl-α-hydroxyacetyl)-L-alaninyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-2), the title compound was prepared as a colorless solid.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.92 (m, 2H), 7.61-7.35 (m, 8H), 7.08 (m, 1H), 5.31 (d, 1H), 4.74 (m, 1H), 3.38 (s, 3H), 1.56 (d, 3H).
30

C₂₆H₂₁F₂N₃O₄ (MW = 477.472); mass spectroscopy (MH⁺) 477.

Anal. Calcd for $C_{26}H_{21}F_2N_3O_4$; C, 65.40 H, 4.43 N, 8.80. Found: C, 65.66 H, 4.71 N, 8.54.

Example 7-4

5

Synthesis of 5-(S)-[N'-(3,5-difluorophenylacetyl)-L-valinyl]amino- 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D above using 3,5-difluorophenylacetic acid and 5-(S)-[L-valinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-C), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $CHCl_3/MeOH$.

10

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.54-7.25 (m, 8H), 6.74 (m, 2H), 6.74 (m, 2H), 6.70 (m, 1H), 6.49 (d, 1H), 5.26 (d, 1H), 4.49 (m, 1H), 3.43 (s, 2H), 3.35 (s, 3H), 2.06 (m, 1H), 0.91 (m, 6H).

15

Optical Rotation: $[\alpha]_{20} = -144$ @ 589 nm ($c = 1$, MeOH).

$C_{28}H_{27}F_2N_3O_3$ (MW = 491.543); mass spectroscopy (MH⁺) 490.9

Anal. Calcd for $C_{28}H_{27}F_2N_3O_3$; C, 68.42 H, 5.54 N, 8.55. Found: C, 68.51 H, 5.82, N, 8.61.

20

Example 7-5

Synthesis of 5-(S)-[N'-(3,5-difluorophenylacetyl)-L-*tert*-leucinyl]amino- 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood) and 5-(S)-[L-*tert*-leucinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-D), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $CHCl_3/MeOH$.

30

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.58-7.36 (m, 9H), 6.80 (m, 2H), 6.72 (m, 1H), 6.25 (d, 1H), 5.27 (d, 1H), 4.52 (d, 1H), 3.53 (s, 2H), 3.35 (s, 3H), 0.97 (m, 9H).

Optical Rotation: $[\alpha]_{20} = -137@ 589 \text{ nm}$ ($c = 1$, MeOH).

$\text{C}_{29}\text{H}_{29}\text{F}_2\text{N}_3\text{O}_4$ (MW = 505.57); mass spectroscopy (MH+) 504.9

Anal. Calcd for $\text{C}_{28}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_4 \cdot \text{H}_2\text{O}$; C, 66.52 H, 5.92 N, 8.02. Found: C, 66.39 H, 5.76, N, 7.79.

5

Example 7-6

Synthesis of

5-(S)-[N'-((S)-3,5-Difluorophenyl- α -hydroxyacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10 Following General Procedure D above using (S)-3,5-difluoromandelic acid and 5-(S)-[L-valinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-C), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $\text{CHCl}_3/\text{MeOH}$.

15 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.78$ (d, 1H), 7.53-7.25 (m, 8H), 6.86 (m, 2H), 6.71 (m, 2H), 5.22 (d, 1H), 4.76 (s, 1H) 4.43 (m, 1H), 3.34 (s, 3H), 2.08 (m, 1H), 0.91 (m, 6H).

$\text{C}_{28}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_4$ (MW = 507.542); mass spectroscopy (MH+) 506.9

20 Anal. Calcd for $\text{C}_{28}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_4$; C, 66.26 H, 5.32 N, 8.27. Found: C, 66.08 H, 5.62, N, 7.97.

Example 7-7

Synthesis of

5-(S)-[N'-((S)-3,5-difluorophenyl- α -hydroxyacetyl)-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 Following General Procedure D above using (S)-3,5-difluoromandelic acid and 5-(S)-[L-*tert*-leucinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-D), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $\text{CHCl}_3/\text{MeOH}$.

30

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.67 (d, 1H), 7.54-7.25 (m, 8H), 6.83 (m, 2H), 6.69 (m, 2H), 5.22 (d, 1H), 4.74 (s, 1H) 4.44 (d, 1H), 3.35 (s, 3H), 0.97 (m, 9H).

C₂₉H₂₉F₂N₃O₄ (MW = 521.569); mass spectroscopy (MH⁺) 520.9

Anal. Calcd for C₂₉H₂₉F₂N₃O₄; C, 66.78 H, 5.60 N, 8.06. Found: C, 66.56 H, 5.85, N, 7.83.

Example 7-8

Synthesis of

5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 5-amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-G), the title compound was prepared as a colorless solid. The product was purified by flash chromatography.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.61-7.215 (m, 8H), 6.76 (m, 2H), 6.68 (m, 1H), 6.53 and 6.40 (two d, 1H), 5.32 (d, 1H), 4.71 (m, 1H) 4.37 (m, 2H), 3.69 (s, 3H), 1.49 and 1.39 (two d, 3H).

C₂₈H₂₅F₂N₃O₅ (MW = 521.518); mass spectroscopy (MH⁺) 522

Anal. Calcd for C₂₈H₂₅F₂N₃O₅ .1.5 mol H₂O; C, 61.30 H, 4.55 N, 7.65. Found: C, 61.30 H, 4.53, N, 7.68.

Example 7-9

Synthesis of

5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-7-(methylcarboxylate)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure II-A, Method B and using 5-[(3,5-difluorophenylacetyl)-L-alaninyl]-amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-8), the title compound was prepared as a colorless solid. The product was purified by flash chromatography.

C₂₇H₂₃F₂N₃O₅ (MW = 507.49); mass spectroscopy (MH⁺) 508

Anal. Calcd for $C_{27}H_{23}F_2N_3O_5 \cdot 2 \text{ mol } H_2O$; C, 59.66 H, 4.23 N, 7.72.

Found: C, 59.88 H, 4.29, N, 7.66.

Example 7-10

5

Synthesis of 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino- 7-(3,3-dimethyl-2-butanoyl)-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one

10 Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 5-amino-7-(3,3-dimethyl-2-butanoyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-H), the title compound was prepared as a colorless solid. The product was purified by flash chromatography.

NMR data was as follows:

15

1H -nmr ($CDCl_3$): δ = 7.57 (m, 3H), 7.41 (m, 5H), 7.14 (m, 1H), 6.78 (m, 2H), 6.68 (m, 1H), 6.44 and 6.26 (two d, 1H), 5.34(d, 1H), 4.68 (m, 1H) 4.59 (m, 2H); 3.52 and 3.47 (two s, 2H), 1.52 and 1.42 (two d, 3H), 1.23 (s, 9H).

$C_{31}H_{31}F_2N_3O_4$ (MW = 547.599); mass spectroscopy (MH⁺) 548

Anal. Calcd for $C_{31}H_{31}F_2N_3O_4 \cdot 0.5 \text{ mol } H_2O$; C, 66.89 H, 5.59 N, 7.54.

20

Found: C, 66.52 H, 5.73, N, 7.18.

Example 7-11

25

Synthesis of 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]amino- 7-(morpholinylacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D using 5-[N'-(3,5-difluorophenylacetyl)-L-alaninyl]-amino-7-(methylcarboxylate)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-9) and morpholine (Aldrich), the title compound was prepared as a colorless foam. The product was purified by flash chromatography.

30

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.57-7.37 (m, 8H), 6.81-6.69 (m, 3H), 5.35 (m, 1H), 4.73- 4.67 (m, 2H), 4.17 (m, 1H), 3.66-3.26 (m, 10 H), 1.46 and 1.40 (two d, 3H).

$C_{31}H_{30}F_2N_4O_5$ (MW = 576.592); mass spectroscopy (MH⁺) 577

Anal. Calcd for $C_{31}H_{30}F_2N_4O_5 \cdot 0.5$ mol H_2O ; C, 63.57 H, 5.12 N, 9.56.

Found: C, 63.41 H, 5.51, N, 8.92.

5

Example 7-12

Synthesis of

5-(S)-(N'-(S)-(+)-2-Hydroxy-3-methylbutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure H using (S)-(+)-2-hydroxy-3-methylbutyric
10 acid (Aldrich) and 5-S-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-B), the title compound was prepared as a white solid. The product was purified by silica gel chromatography using gradient elution of MeOH/ CH_2Cl_2 (1:99 -3:97).

NMR data was as follows:

15 ¹H-nmr ($CDCl_3$): δ = 7.94 (d, J = 7.0 Hz, 1H), 7.55-7.22 (m, 9H), 5.25 (d, J = 7.5 Hz, 1H), 4.79-4.75 (m, 1H), 3.83 (d, J = 3.1 Hz, 1H), 3.78 (br s, 1H), 3.32 (s, 3H), 2.08-2.01 (m, 1H), 1.36 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H).

$C_{23}H_{27}N_3O_4$ (MW = 409.48); mass spectroscopy (MH⁺) 410.4.

20 Anal Calcd for $C_{23}H_{27}N_3O_4$, C, 67.46; H, 6.65; N, 10.26; Found: C, 67.59; H, 6.66; N, 10.34.

Example 7-13

Synthesis of

25 5-[N'-Cyclopentyl- α -hydroxyacetyl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D above using cyclopentyl- α -hydroxyacetic acid (Example P) and 5-(S)-[L-valinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-C), the title compound was
30 prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $CHCl_3$ /MeOH.

$C_{27}H_{33}N_3O_4$ (MW = 463.5); mass spectroscopy (MH⁺) 464.

Anal. Calcd for $C_{27}H_{33}N_3O_4$; C, 69.96 H, 7.18 N, 9.06. Found: C, 69.72 H, 6.99, N, 8.91.

Example 7-14

Synthesis of

5-(S)-(N'-((S)-3,3-dimethyl-2-hydroxybutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
and

5-(S)-(N'-((R)-3,3-dimethyl-2-hydroxybutyryl)-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure H using 2-hydroxy-3,3-dimethylbutyric acid (Aldrich) and 5-(S)-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-B), the title compound was prepared as a white solid. The product was purified by silica gel chromatography using gradient elution of MeOH/ CH_2Cl_2 (1:99 -3:97).

NMR data for isomer 1 was as follows:

1H -nmr ($CDCl_3$): δ = 7.90 (d, J = 6.6 Hz, 1H), 7.57-7.24 (m, 8H), 6.99 (d, J = 7.5 Hz, 1H), 5.24 (d, J = 6.5 Hz, 1H), 4.83-4.76 (m, 1H), 3.69 (s, 1H), 3.32 (s, 3H), 3.19 (br s, 1H), 1.39 (d, J = 7.0 Hz, 3H), 0.96 (s, 9H).

$C_{24}H_{29}N_3O_4$ (MW = 423.51); mass spectroscopy (MH^+) 424.1.

Anal Calcd for $C_{24}H_{29}N_3O_4$ (isomer 1), C, 68.07; H, 6.90; N, 9.92; Found: C, 68.22, H, 7.04; N, 9.91.

NMR data for isomer 2 was as follows:

1H -nmr ($CDCl_3$): δ = 8.00-7.99 (m, 1H), 7.97-7.30 (m, 8H), 7.03-7.00 (m, 1H), 5.25 (d, J = 7.0 Hz, 1H), 4.82-4.75 (m, 1H), 3.69 (s, 1H), 3.33 (s, 3H), 2.66 (br s, 1H), 1.48 (d, J = 7.0 Hz, 3H), 0.98 (s, 9H).

$C_{24}H_{29}N_3O_4$ (MW = 423.51); mass spectroscopy (MH^+) 424.1.

Anal Calcd for $C_{24}H_{29}N_3O_4$ (isomer 2), C, 68.07; H, 6.90; N, 9.92; Found: C, 67.77, H, 7.08; N, 9.66.

Example 7-15

Synthesis of

5-[N'-Cyclopentyl- α -hydroxyacetyl]-L-*tert*-leucinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5 Following General Procedure D above using cyclopentyl- α -hydroxyacetic acid (Example P) and 5-(S)-[L-*tert*-leucinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-D), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 CHCl₃/MeOH.

10 C₂₈H₃₅N₃O₄.(477.6); mass spectroscopy (MH+) 478.

Anal. Calcd for C₂₈H₃₅N₃O₄; C, 66.39 H, 5.57 N, 11.06. Found: C, 66.33 H, 5.67, N, 10.89.

Example 7-16

15

Synthesis of

5-[N'-Cyclopentyl- α -hydroxyacetyl]-L-alaninyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20 Following General Procedure D above using cyclopentyl- α -hydroxyacetic acid (Example P) and 5-(S)-[L-alaninyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-B), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 99:1 CHCl₃/MeOH.

NMR data was as follows:

25 ¹H-nmr (CDCl₃): δ = 7.78 (m, 2H), 7.62-7.28 (m, 8H), 7.08 and 6.99 (two d, 1H), 5.27 (d, 1H), 4.78 (m, 1H), 4.06 (m, 1H), 3.34 (s, 3H), 2.54 (m, 2H), 2.29 (m, 1H), 1.76-1.48 (m, 6H) 1.43 (d, 3H).

C₂₅H₂₉N₃O₄.(435.52); mass spectroscopy (MH+) 436

Anal. Calcd for C₂₅H₂₉N₃O₄; C, 68.95 H, 6.71 N, 9.65. Found: C, 69.06 H, 6.89, N, 9.51.

30

Example 7-17

Synthesis of
5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-
5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

5 Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 5-amino-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one hydrochloride (prepared using the compound of Example 7-E, followed by Boc removal as in Example 7-B, Step B), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 95:5
10 CHCl₃/MeOH.

NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 8.86 (m, 1H), 8.75 (m, 1H), 8.49 (m, 1H), 7.78-7.23 (m, 8H), 7.09 (m, 1H), 7.03 (m, 2H), 5.07 (m, 1H), 4.60 (m, 1H), 3.55 (s, 2H), 1.32 (d, 3H).

15 C₂₅H₂₁F₂N₃O₃ (449.45); mass spectroscopy (MH⁺) 450.

Anal. Calcd for C₂₅H₂₁F₂N₃O₃; C, 66.81 H, 4.71 N, 9.35. Found: C, 67.11 H, 4.84, N, 9.09.

Example 7-18

Synthesis of
5-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-
7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20 Following General Procedure D above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 5-amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-F), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 99:1 CHCl₃/MeOH.

NMR data was as follows:

30 ¹H-nmr (CDCl₃): δ = 7.58-7.33 (m, 4H), 7.40 (m, 4H), 6.81 (m, 2H), 6.71 (m, 1H), 6.34 and 6.27 (two d, 1H), 5.22 (d 1H), 4.69 (m, 1H), 4.27 (m, 1H), 3.52 (s, 2H), 3.33 (m, 1H), 1.52 and 1.42 (two d, 3H), 0.57 and 0.29 (two d, 3H).

C₂₉H₂₉F₂N₃O₃ (MW = 505.562); mass spectroscopy (MH⁺) 505.

Anal. Calcd for $C_{29}H_{29}F_2N_3O_3$; C, 68.89 H, 5.78 N, 8.31. Found: C, 69.01 H, 6.02 N, 8.33.

Example 7-19

Synthesis of

5-[N'-(2-Hydroxy-3-methylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D above using 2-hydroxy-3-methylbutyric acid (Aldrich) and 5-(S)-[L-valinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-C), the title compound was prepared as a colorless solid. The product was purified by flash chromatography using 98:2 $CHCl_3/MeOH$.

NMR data was as follows:

1H -nmr ($CDCl_3$): δ = 7.69-7.25 (m, 8H), 7.08 and 6.92 (two d, 1H), 5.29 (d, 1H), 4.54 (m, 1H), 4.01 (m, 1H), 3.36 (s, 3H), 2.12 (m, 2H), 0.99 (m, 6H), 0.83 (m, 6H).

$C_{25}H_{31}N_3O_4$ (437.537); mass spectroscopy (MH⁺) 438.

Anal. Calcd for $C_{25}H_{31}N_3O_4$; C, 68.63 H, 7.14 N, 9.60. Found: C, 68.71 H, 6.99, N, 9.42.

Example 7-20

Synthesis of

5-(S)-[N'-((S or R)-2-Hydroxy-3,3-dimethylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

and

5-(S)-[N'-((S or R)-2-Hydroxy-3,3-dimethylbutyryl)-L-valinyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D above using 2-hydroxy-3,3-dimethylbutyric acid (Aldrich) and 5-(S)-[L-valinyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-C), the title compound was prepared as a colorless solid. The diastereomers were purified by flash chromatography using 99:1 $CHCl_3/MeOH$.

Isomer 1:

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.60-7.28 (m, 8H), 6.63 (d, 1H), 5.26 (d, 1H), 4.53 (m, 1H), 3.74 (s, 1H), 3.35 (s, 3H), 2.12 (m, 1H), 0.998 (m, 15H).

C₂₆H₃₃N₃O₄ (MW = 451); mass spectroscopy (MH⁺) 452.

Anal. Calcd for C₂₆H₃₃N₃O₄ 0.5 mol H₂O; C, 67.80 H, 7.16 N, 9.11.

5 Found: C, 68.32 H, 7.06 N, 8.91.

Isomer 2:

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.59-7.28 (m, 8H), 6.82 (d, 1H), 5.25 (d, 1H), 4.52(m,1H), 3.74 (s, 1H), 3.33 (s, 3H), 2.16 (m, 1H), 0.997 (m, 15H).

10 C₂₆H₃₃N₃O₄ (MW = 451); mass spectroscopy (MH⁺) 452

Anal. Calcd for C₂₆H₃₃N₃O₄; C, 69.16 H, 7.37 N, 9.31. Found: C, 69.33 H, 7.49 N, 9.22.

Example 7-22

15

Synthesis of

5-{N'-(4-Phenyl-furazan-3-yl)alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-(4-phenyl-furazan-3-yl)alanine (Example I) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-A), the title compound was prepared. The reaction was monitored by tlc (R_f = 0.75, 5% MeOH/CHCl₃) and product was purified by chromatography (silica, CHCl₃).

20

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 4.52 (m, 1H); 4.87 (t, 1H).

25

MW = 453.50; mass spectroscopy (M⁺) 454.

Example 7-23

Synthesis of

5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one

30

Following Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one (Example 7-Z), the title compound was prepared.

The reaction was monitored by tlc ($R_f = 0.3$, 4% MeOH/ CHCl_3) and product was purified by chromatography (silica, 4% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.54$ (s, 2H); 1.36 (m, 3H).

5 MW = 475.58; mass spectroscopy (MH+) 476.

Example 7-24

Synthesis of

10 **5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-K), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.35$, 3% MeOH/ CHCl_3) and product was purified by chromatography (silica, 3% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 4.68$ (m, 1H); 6.32 (dd, 1H).

MW = 581.66; mass spectroscopy (M+) 582.

20 Example 7-25

Synthesis of

5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-L), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.30$, 5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 3% MeOH/ CHCl_3).

NMR data was as follows:

30 ^1H -nmr (CDCl_3): $\delta = 4.07$ (m, 1H); 4.70 (m, 1H); 5.24 (d, 1H).

MW = 503.55; mass spectroscopy (M+) 504.

Example 7-26

Synthesis of
5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-
7-(2',2',2'-trifluoroethyl)-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-M), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.15$, 5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 5% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 4.07$ (m, 1H); 4.69 (m, 1H); 5.02 (m, 1H); 5.37 (d, 1H).

MW = 531.48; mass spectroscopy (MH⁺) 530.

Example 7-27

Synthesis of
5-{N'-(3,5-Difluorophenylacetyl)-L-alaninyl}amino-
7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-(3,5-difluorophenylacetyl)-L-alanine (Ex. B) and 5-amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-N), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.35$, 5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 5% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 1.43$ (dd, 3H); 3.94 (m, 1H); 4.68 (m, 1H); 5.18 (d, 1H).

MW = 531.60; mass spectroscopy (M⁺) 533.

Example 7-28

Synthesis of
5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}amino-
9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-O), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.4$, 10% MeOH/CHCl₃) and product was purified by chromatography (silica, 2.5% MeOH/CHCl₃).

NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 3.36$ (s, 3H); 4.67 (m, 1H); 5.05 (s, 1H); 5.21 (m, 1H).

MW = 497.47; mass spectroscopy (M⁺) 498.

Example 7-29

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-P), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.4$, 10% MeOH/CHCl₃) and product was purified by 2.5% chromatography (silica, MeOH/CHCl₃).

NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 1.45$ (dd, 3H); 3.31 (d, 3H).

MW = 497.47; mass spectroscopy (MH⁺) 498.

Example 7-30

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-Q), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.4$, 10% MeOH/CHCl₃) and product was purified by chromatography (silica, 2.5% MeOH/CHCl₃).

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.44 (dd, 3H); 3.35 (d, 3H).

MW = 497.47; mass spectroscopy (M+) 498.

Example 7-31

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-R), the title compound was prepared. The product was purified by chromatography (silica, 2.5% MeOH/CHCl₃).

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.48 (dd, 3H); 3.45 (m, 1H).

MW = 519.55; mass spectroscopy (M+) 520.

Example 7-32

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-alaninyl}amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-alaninyl)-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-S), the title compound was prepared. The product was purified by chromatography (silica, 1-2% MeOH/CHCl₃).

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.48 (dd, 3H); 5.04 (d, 1H).

MW = 597.66; mass spectroscopy (M+) 599.

Example 7-33

Synthesis of

5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-valinyl)-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-T), the title compound was prepared. The reaction was monitored by tlc ($R_f = 0.3$, 2.5% MeOH/ CHCl_3) and product was purified by chromatography (silica, 2.5% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.42$ (m, 1H); 4.07 (m, 1H); 5.03 (d, 1H).

Example 7-34

10

Synthesis of 5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino- 7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-valinyl)-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-U), the title compound was prepared. The product was purified by chromatography (silica, 1-2% MeOH/ CHCl_3).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.54$ (m, 1H); 4.35 (m, 1H); 5.03 (d, 1H).

20

MW = 625.71; mass spectroscopy (M^+) 625.

Example 7-35

25

Synthesis of 5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino- 7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid (Example L) and 5-(L-valinyl)-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-V), the title compound was prepared. The product was purified by chromatography (silica, 5% MeOH/ CHCl_3).

30

NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): $\delta = 4.25$ (m, 1H); 4.52 (m, 1H); 5.05 (t, 1H); 5.24 (2 doublets, 1H).

MW = 577.67; mass spectroscopy (M^+) 578.

Example 7-36

Synthesis of
5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino-
10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5 Following General Procedure D and using (S)-3,5-difluoromandelic acid
(Example L) and 5-(L-valinyl)-amino-10-fluoro-7-methyl-5,7-dihydro-6H-
dibenz[b,d]azepin-6-one hydrochloride (Example 7-W), the title compound was
prepared. The product was purified by chromatography (silica, 2.5%
MeOH/CHCl₃).

10 Anal. Calc.: C, 71.02; H, 5.96; N, 6.72. Found: C, 71.10, H, 6.12, N, 6.63.

Example 7-37

Synthesis of
5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino-
15 13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid
(Example L) and 5-(L-valinyl)-amino-13-fluoro-7-methyl-5,7-dihydro-6H-
dibenz[b,d]azepin-6-one hydrochloride (Example 7-X), the title compound was
prepared. The product was purified by chromatography (silica, 2.5%
20 MeOH/CHCl₃).

Anal. Calc.: C, 71.02; H, 5.96; N, 6.72. Found: C, 71.10, H, 6.12, N, 6.63.

Example 7-38

Synthesis of
25 5-{N'-[(S)-3,5-Difluoromandelyl]-L-valinyl}amino-
9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using (S)-3,5-difluoromandelic acid
(Example L) and 5-(L-valinyl)-amino-9-fluoro-7-methyl-5,7-dihydro-6H-
dibenz[b,d]azepin-6-one hydrochloride (Example 7-Y), the title compound was
30 prepared. The product was purified by chromatography (silica, 2.5%
MeOH/CHCl₃).

Anal. Calc.: C, 71.02; H, 5.96; N, 6.72. Found: C, 71.10, H, 6.12, N, 6.63.

8. Benzodiazepine Derivatives and Related Compounds

GENERAL PROCEDURE 8-A

N-1-Methylation of Benzodiazepines

5 A solution of benzodiazepine (1 eq.) in DMF (0.1 M concentration) at 0°C was treated with potassium tert-butoxide (1.0 eq., 1.0 M solution in THF). After stirring for 30 minutes at 0°C, iodomethane (1.3 eq.) was added and stirring continued for 25 minutes. The mixture was diluted with methylene chloride and washed with water and brine. The organic phase was dried over
10 Na₂SO₄, filtered, and concentrated. The crude product was then either purified by trituration with 1:1 ether/hexanes or chromatographed via HPLC using ethyl acetate/hexanes as the eluent.

GENERAL PROCEDURE 8-B

15 Cbz Removal Procedure

A flask was charged with the Cbz-protected 3-aminobenzodiazepine (1 eq.). To this was added HBr (34 eq.; 30% solution in acetic acid). Within 20 minutes all of the starting material dissolves. The reaction was stirred for 5 hours at ambient temperature. Ether was added to the orange solution causing the
20 HBr•amine salt to precipitate. The mixture was decanted. This process of adding ether and decanting was repeated thrice in an effort to remove acetic acid and benzyl bromide. Toluene was added and the mixture concentrated *in vacuo*. This step was also repeated. The HBr salt was partitioned between ethyl acetate and 1 M K₂CO₃. The aqueous layer was back-extracted with ethyl acetate. The
25 combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated.

GENERAL PROCEDURE 8-C

Boc Removal Procedure

30 A solution of Boc-protected amine (1 eq.) in methylene chloride (0.15 M concentration) was cooled to 0°C and treated with trifluoroacetic acid (30 eq.).

After 10 minutes at 0°C, the cooling bath was removed and stirring continued at ambient for 20 minutes to 1 hour. The mixture was concentrated *in vacuo* to remove excess trifluoroacetic acid. The residue was dissolved in methylene chloride and washed with saturated aqueous NaHCO₃ or 1 M K₂CO₃ and brine.
5 The organic layer was dried over Na₂SO₄, filtered, and concentrated.

GENERAL PROCEDURE 8-D

Azide Transfer Reaction Using KHMDS

The azido derivative was prepared using the procedure described in John W.
10 Butcher et al., *Tet. Lett.*, **37**, 6685-6688 (1996).

GENERAL PROCEDURE 8-E

Azide Transfer Reaction Using LDA

To a solution of diisopropylamine (1.1 eq.) in 1 mL of dry THF cooled to -
15 78°C was added n-butyl lithium (1.6M in hexane) (1.1 eq.) dropwise maintaining the reaction temperature at -78°C. The reaction mixture was stirred for 30 min. at -78°C and then the lactam (0.471 mM) was added dropwise as a solution in 1 mL of dry THF. The reaction mixture was stirred at -78°C for 30 min. and then
20 a pre-cooled solution of trisyl azide (1.2 eq.) was added as a solution in 1 mL of dry THF. The reaction mixture was stirred at -78°C for 20 min. and then quenched with acetic acid (4.0 eq.). The reaction mixture was then stirred at 40°C for 2 hrs. The reaction was then poured into EtOAc and washed with water, sodium bicarbonate and brine, and then dried over sodium sulfate, filtered and concentrated. The residue was purified by LC 2000 chromatography.

25

GENERAL PROCEDURE 8-F

Azido Group Reduction

The azido group was reduced to the corresponding primary amine using the procedure described in John W. Butcher et al., *Tet. Lett.*, **37**, 6685-6688 (1996).
30

GENERAL PROCEDURE 8-G

N-Alkylation of Amides or Lactams Using Sodium Hydride or Potassium tert-Butoxide

To a slurry of sodium hydride or potassium tert-butoxide (1.1 eq) in 15 mL
5 of dry DMF was added the appropriate amide (0.0042 moles) as a solution in 10
mL of DMF. The alkyl iodide was then added and a thick slurry resulted. The
reaction became less thick as time elapsed and when complete by TLC the
reaction had become homogeneous. The reaction mixture was poured over ice
and extracted into ethyl acetate. The organic layer was washed with water,
10 followed by brine. The organic layer was then dried over sodium sulfate,
filtered and concentrated under reduced pressure. The residue was purified by
HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

GENERAL PROCEDURE 8-H

15 N-Alkylation of Amides or Lactams Using KHMDS

To the appropriate amide or lactam in THF cooled to -78°C was added
KHMDS dropwise and the reaction mixture was stirred for 30 min. at -78°C .
The alkyl iodide was then added dropwise while maintaining the temperature at
20 -70°C . The cooling bath was then removed and reaction was allowed to warm
to room temperature and stirring was continued for 2 hours. The reaction
mixture was then poured over ice and extracted into ethyl acetate. The organic
extracts were washed with water, followed by brine. The organic layer was then
dried over sodium sulfate, filtered and concentrated under reduced pressure. The
25 residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane
system.

GENERAL PROCEDURE 8-I

N-Alkylation of Amides or Lactams Using Cesium Carbonate

30 To a solution of the amide or lactam in DMF was added cesium carbonate
(1.05 eq) and an alkyl iodide (1.1 eq). The mixture was allowed to stir
overnight at room temperature and then the reaction mixture was diluted with

ethyl acetate and washed with water, followed by brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

5

GENERAL PROCEDURE 8-J

BOC Removal Procedure

To an N-Boc protected compound was added $\text{CH}_2\text{Cl}_2/\text{TFA}$ (4:1) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then concentrated. The residue was extracted into dichloromethane and washed with water, saturated sodium bicarbonate, dried over Na_2SO_4 , filtered and concentrated to give the free amine.

10

GENERAL PROCEDURE 8-K

15

Azide Transfer Procedure

This azide transfer procedure is a modification of the procedure described in Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* 1990, 112, 4011-4030. To a solution of the lactam substrate (1.0 eq.) in THF (~0.1 M) under N_2 at -78°C was added a solution of $\text{KN}(\text{TMS})_2$ (1.1 eq. of 0.5 M in Toluene, Aldrich) dropwise over a period of 2-10 minutes. A slight exotherm was often observed by an internal thermometer, and the resulting solution was stirred for 5-15 minutes, while re-cooling to -78°C . Then, trisyl azide (1.1-1.5 eq., CAS No. 36982-84-0, prepared as described by references in the Evans reference above) in THF (~0.5 M), either precooled to -78°C or at room temperature, was added via cannula over a period of 0.5-5 minutes. Again, a slight exotherm was generally noted. The resulting solution was stirred for from 5-10 minutes, while re-cooling to -78°C . Then, AcOH (4.5-4.6 eq., glacial) was added, the cooling bath removed and the mixture allowed to warm to room temperature with stirring for 12-16 hours. The mixture was diluted with EtOAc, in a 2-5 volume multiple of the initial THF volume, and washed with dilute aq. NaHCO_3 (1-2x), 0.1-1.0 M aq. HCl (0-2x), and brine (1x). The

20

25

30

organic phase was then dried over MgSO_4 , filtered, concentrated to provide the crude product.

GENERAL PROCEDURE 8-L

5

Azide Reduction to an Amine

A mixture of the azide in absolute EtOH (0.03-0.07 M) and 10% Pd/C (~1/3 by weight of the azide) was shaken in a Parr apparatus under H_2 (35-45 psi) at room temperature for 3-6 hours. The catalyst was removed by filtration through a plug of Celite, rinsing with absolute EtOH, and the filtrate
10 concentrated to provide the crude amine product.

GENERAL PROCEDURE 8-M

Amide Alkylation Using Cesium Carbonate

This procedure is a modification of the procedure described in Claremon, D. A.; et al, PCT Application: WO 96-US8400 960603. To a mixture of 2,4-
15 dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 49799-48-6) in DMF (1.0 eq., 0.7 M) under N_2 at room temperature was added Cs_2CO_3 (2.2 eq.) and the appropriate alkyl halide (2.2 eq.). The mixture was stirred at room temperature for 5.5-16 hours. The mixture was partitioned between EtOAc and
20 sat. NaHCO_3 . The aqueous layer was extracted with EtOAc (1-2x) and the combined EtOAc extracts were dried over Na_2SO_4 , filtered, and concentrated to provide the crude product.

GENERAL PROCEDURE 8-N

25

BOC Removal Procedure

A stream of anhydrous HCl gas was passed through a stirred solution of the N-t-Boc protected amino acid in 1,4-dioxane (0.03-0.09 M), chilled in a ice bath to $\sim 10^\circ\text{C}$ under N_2 , for 10-15 minutes. The solution was capped, the cooling bath removed, and the solution was allowed to warm to room temperature with
30 stirring for 2-8 hours, monitoring by TLC for the consumption of starting material. The solution was concentrated (and in some instances dissolved in

CH_2Cl_2 then re-concentrated and placed in vacuum oven at 60-70°C to remove most of the residual dioxane) and used without further purification.

Example 8-A

Synthesis of

3-Amino-1,3-dihydro-5-(1-piperidinyl)-2H-1,4-benzodiazepin-2-one

Step A - Preparation of 1,2-Dihydro-3H-1-methyl-5-(1-piperidinyl)-1,4-benzodiazepin-2-one

A solution of phosphorous pentachloride (1.2 eq) in methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (Showell, G. A.; Bourrain, S.; Neduvilil, J. G.; Fletcher, S. R.; Baker, R.; Watt, A. P.; Fletcher, A. E.; Freedman, S. B.; Kemp, J. A.; Marshall, G. R.; Patel, S.; Smith, A. J.; Matassa, V. G. *J. Med. Chem.* **1994**, 37, 719.) in methylene chloride. The resultant yellowish-orange solution was stirred at ambient temperature for 2.5 hours; the solvent was removed *in vacuo*. The orange residue was redissolved in methylene chloride, cooled to 0 °C, and treated with a solution of piperidine (2 eq) and triethylamine (2 eq) in methylene chloride. The cooling bath was removed and the reaction stirred for 18 hours. The reaction mixture was washed with saturated aqueous NaHCO_3 (back-extracted with methylene chloride) and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC eluting with a gradient of 4 to 10% methanol/methylene chloride affording the title intermediate as a yellow solid having a melting point of 103-105°C.

$\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}$ (MW 257.37); mass spectroscopy 257.

Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.94; H, 7.58; N, 16.23.

Step B - Preparation of 1,2-Dihydro-3H-1-methyl-3-oximido-5-(1-piperidinyl)-1,4-benzodiazepin-2-one

Potassium tert-butoxide (2.5 eq) was added in two portions to a -20°C solution of 1,2-dihydro-3H-1-methyl-5-(1-piperidinyl)-1,4-benzodiazepin-2-one.

(1 eq) in toluene). After stirring at - 20°C for 20 min, isoamyl nitrite (1.2 eq.; Aldrich) was added to the red reaction mixture. The reaction was stirred at -20 °C for 5 hours at which time the reaction was done by TLC. The cooling bath was removed and the reaction quenched with 0.5 M citric acid. After stirring for 10 minutes, diethyl ether was added. The suspension was stirred at ambient temperature overnight then filtered washing with ether. The resultant cream colored solid had a melting point of 197-200°C.

¹H NMR data of the E/Z isomers was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.64 (1H, bs), 7.48 (2H, d, J=7.4 Hz), 7.35-7.20 (6H, m), 6.75 (1H, bs), 3.8-3.2 (8H, m), 3.46 (3H, s), 3.42 (3H, s), 1.90-1.40 (12H, m).

C₁₅H₁₈N₄O₂ (MW = 286.37); mass spectroscopy 286.

Step C - Preparation of 1,2-dihydro-3H-1-methyl-3-[O-(ethylaminocarbonyl)oximido]-5-(1-piperidinyl)-1,4-benzodiazepin-2-one

A mixture of 1,2-dihydro-3H-1-methyl-3-oximido-5-(1-piperidinyl)-1,4-benzodiazepin-2-one (1 eq) in THF was treated with ethyl isocyanate (1.7 eq) and triethylamine (0.6 eq). The mixture was heated to 64°C for 4 hours. The mixture was concentrated and the residue purified by HPLC eluting with 5% methanol/methylene chloride.

¹H NMR data of the E/Z isomers was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.50 (2H, dd, J=8.4, 1.5 Hz), 7.35-7.22 (6H, m), 6.42 (1H, bt), 6.20 (1H, bt), 3.7-3.4 (8H, m), 3.46 (3H, s), 3.44 (3H, s), 3.25 (4H, m), 1.9-1.4 (12H, m), 1.12 (3H, t, J=6.3 Hz), 1.10 (3H, t, J=6.3 Hz).

C₁₈H₂₃N₅O₃ (MW = 357.46); mass spectroscopy 357.

Step D - Preparation of 3-Amino-1,3-dihydro-2H-1-methyl-5-(1-piperidinyl)-1,4-benzodiazepin-2-one

The 1,2-dihydro-3H-1-methyl-3-[O-(ethylaminocarbonyl)oximido]-5-(1-piperidinyl)-1,4-benzodiazepin-2-one (1 eq) was hydrogenated in methanol over

5% palladium on carbon (0.15 eq) at 43 psi for 3.25 hours. The reaction was filtered through celite and concentrated *in vacuo*. The residue was taken up in methylene chloride and filtered a second time through celite. The filtrate was concentrated and the resultant foam was used immediately.

Example 8-B

Synthesis of
3-(L-Alaninyl)-amino-2,3-dihydro-
1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

10 Step A - Preparation of (S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate

15 The title intermediate was prepared according to Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. *J. Org. Chem.* **1987**, *52*, 955 using 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Bock M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Hirshfield, J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 3232.) as the starting material.

20 Step B - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-alanine following General Procedure D.

$C_{24}H_{28}N_4O_4$ (MW = 436.56); mass spectroscopy 436.

Anal. Calc. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.79; H, 6.68; N, 12.80.

30

Step C - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title compound was prepared as a white foam.

Anal. Calc. for $C_{19}H_{19}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 70.11; H, 6.85; N, 15.01.

Example 8-C

Synthesis of

3-(L-Alaninyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

A solution of 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-5-phenyl-1H-1,4-Benzodiazepin-2-one (1 eq; Neosystem) in DMF was cooled to 0°C and treated with potassium *tert*-butoxide (1 eq; 1.0M solution in THF). The resultant yellow solution was stirred at 0°C for 30 minutes then quenched with methyl iodide (1.3 eq). After stirring an addition 25 minutes the reaction was diluted with methylene chloride and washed with water and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC chromatography eluting with a gradient of 20→30% ethyl acetate/hexanes.

$C_{24}H_{20}ClN_3O_3$ (MW = 433.92); mass spectroscopy 433.

Anal. calcd for $C_{24}H_{20}ClN_3O_3$: C, 66.44; H, 4.65; N, 9.68. Found: C, 66.16; H, 4.50; N, 9.46.

Step B - Preparation of 3-Amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

Step C - Preparation of 3-[N'-tert-Butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure D using N-Boc-L-alanine and 3-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{28}ClN_4O_4$ (MW = 471.18); mass spectroscopy 471

Anal. calcd for $C_{24}H_{28}ClN_4O_4$: C, 61.21; H, 5.78; N, 11.90. Found: C, 61.24; H, 5.59; N, 11.67.

Step D - Preparation of 3-(L-Alaninyl)amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-tert-butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-D

Synthesis of

3-(L-Alaninyl)amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white foam.

$C_{24}H_{19}BrFN_3O_3$ (MW = 496.36); mass spectroscopy 497.

Anal. calcd for $C_{24}H_{19}BrFN_3O_3$: C, 58.08; H, 3.86; N, 8.47. Found: C, 57.90; H, 4.15; N, 8.20.

Step B - Preparation of 3-Amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

5

Step C - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure D using N-Boc-L-alanine (Novo) and 3-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{26}BrFN_4O_4$ (MW = 533.12); mass spectroscopy 533.2.

Anal. calcd for $C_{24}H_{26}BrFN_4O_4$: C, 54.04; H, 4.91; N, 10.50. Found: C, 53.75; H, 4.92; N, 10.41.

15

Step D - Preparation of 3-(L-Alaninyl)-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

25

Example 8-E

Synthesis of 3-(N'-Methyl-L-alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-[N'-(*tert*-Butylcarbamate)-N'-methyl-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

30

Following General Procedure D and using (S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Example 8-B) and N-*tert*-Boc-N-methyl-alanine (Sigma), the title intermediate was obtained as a white solid.

$C_{25}H_{30}N_4O_4$ (MW = 450.2); mass spectroscopy (M+1) 451.2.

Anal. calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.66; H, 6.89; N, 12.21.

5 Step A - Preparation of 3-(N'-Methyl-L-alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-N'-methyl-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{20}H_{22}N_4O_2$ (MW = 350.46); mass spectroscopy (M+1) 351.4.

10 Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found, C, 68.36; H, 6.20; N, 15.79.

Example 8-F

15 **Synthesis of**
3-(L-Alaninyl)amino-7-chloro-2,3-dihydro-
1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one

20 Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white solid having a melting point of 232-233°C.

$C_{24}H_{19}Cl_2N_3O_3$ (MW = 468.36); mass spectroscopy 468.

25 1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (1H, m), 7.52 (1H, dd, $J=2.4$, 8.7 Hz), 7.42-7.26 (9H, m), 7.07 (1H, d, $J=2.4$ Hz), 6.70 (1H, d, $J=8.3$ Hz), 5.35 (1H, d, $J=8.4$ Hz), 5.14 (2H, ABq, $J=19.6$ Hz), 3.47 (3H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.66, 165.65, 155.72, 140.52, 136.99, 136.0, 132.87, 131.99, 131.47, 131.40, 131.38, 131.16, 130.54, 130.06, 128.45, 128.08, 128.03, 127.72, 127.22, 123.28, 122.01, 68.95, 67.02, 35.32.

30 Step B - Preparation of 3-Amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

5

Step C - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure D using N-Boc-L-alanine and 3-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

10

$C_{24}H_{26}Cl_2N_4O_4$ (MW = 505.44); mass spectroscopy 505.2.

Step D - Preparation of 3-(L-Alaninyl)-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

15

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

20

Example 8-G

Synthesis of

3-(L-Alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-Benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

25

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white solid having a melting point of 205-206°C.

30

$C_{24}H_{27}N_3O_3$ (MW = 405.54); mass spectroscopy 405.

1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (1H, d, J =7.9 Hz), 7.48 (1H, d, J =7.7 Hz), 7.36-7.26 (7H, m), 6.54 (1H, d, J = 8.3 Hz), 5.15 (1H, d, J =8.0 Hz), 5.09

(2H, ABq, $J=17.1$ Hz), 3.39 (3H, s), 2.77 (1H, m), 2.01 (1H, bd, $J=13.6$ Hz), 1.85 (1H, bd, $J=12.4$ Hz), 1.68-1.49 (4H, m), 1.34-1.02 (4H, m).

5 Step B - Preparation of 3-Amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

10 $C_{16}H_{21}N_3O$ (MW+H = 272.1763); mass spectroscopy 272.1766

 Step C - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

15 Following General Procedure D using N-Boc-L-alanine and 3-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{34}N_4O_4$ (MW = 442.62); mass spectroscopy (M+H) 443.2.

20 Step D - Preparation of 3-(L-Alaninyl)amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was
25 used immediately.

$C_{19}H_{26}N_4O_2$ (M+H = 343.2136); mass spectroscopy found 343.2139.

Example 8-H

30 Synthesis of
 3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

 Step A - Preparation of 2-[N-(α -Isopropylthio)-N'-(benzyloxycarbonyl)-glycinyl]-amino-5-nitrobenzophenone

A solution of α -(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* 1975, 31, 863.) in dry THF was cooled to 0 °C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C, the cooling bath was removed and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C. A solution of 2-amino-5-nitrobenzophenone (0.9 eq.; Acros) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous NaHCO₃, and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15→20% ethyl acetate/hexanes giving an off-white foam.

C₂₆H₂₅N₃O₆S (MW = 507.61); mass spectroscopy found 507.9.

Anal. calcd for C₂₆H₂₅N₃O₆S: C, 61.53; H, 4.96; N, 8.28. Found: C, 61.70; H, 4.99; N, 8.22.

Step B - Preparation of 2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone

Ammonia gas was bubbled into a solution 2-[N-(α -isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone (1 eq) in THF at 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4 hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated *in vacuo*. The crude solid was used in step C without further purification.

Step C - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone (1 eq) was treated with glacial acetic acid and ammonium

acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 hours. After concentrating the reaction in vacuo, the residue was partitioned between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over
5 Na_2SO_4 , filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

$\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_5$ (MW = 430.45); mass spectroscopy found (M+H) 431.2.

Anal. calcd for $\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_5$: C, 64.18; H, 4.22; N, 13.02. Found: C,
10 64.39; H, 4.30; N, 13.07.

Step D - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-
15 2,3-dihydro-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

$\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_5$ (MW = 444.48); mass spectroscopy found (M+H) 445.2.

Anal. calcd for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_5$: C, 64.86; H, 4.54; N, 12.60. Found: C,
20 65.07; H, 4.55; N, 12.46.

Step E - Preparation of 3-Amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-
2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title
25 intermediate was prepared as a yellow foam which was used immediately in Step F.

Step F - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

30

Following General Procedure D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

$C_{24}H_{27}N_5O_6$ (MW = 481.56); mass spectroscopy found (M+H) 482.3.

Anal. calcd for $C_{24}H_{27}N_5O_6$: C, 59.88; H, 5.61; N, 14.55. Found: C, 60.22; H, 5.75; N, 13.91.

5 Step G - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material
10 was used immediately.

Example 8-I

Synthesis of

15 3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

A flask was charged with 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (1 eq.;
20 Example 8-D, Step A) and 10% palladium on carbon. Methanol was added, and the flask was placed under a balloon of H_2 . The reaction was stirred for 21 hours. The mixture was filtered through celite washing with methanol. The filtrate was concentrated to a white solid.

$C_{16}H_{14}FN_3O$ (MW = 283.33); mass spectroscopy found (M+H) 284.1.

25 Step B - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title
30 intermediate was prepared as a white solid.

$C_{24}H_{27}FN_4O_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.4.

Anal. calcd for $C_{24}H_{27}FN_4O_4$: C, 63.44; H, 5.95; N, 12.33. Found: C, 63.64; H, 6.08; N, 12.16.

Step C - Preparation of 3-(L-Alaninyl)-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-J

Synthesis of
3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 2-Amino-3'-fluorobenzophenone

A solution of 3-bromofluorobenzene (1 eq.) in THF was cooled to -78°C under nitrogen and treated with *tert*-butyllithium (2.05 eq., 1.6 M solution in pentane) at a rate of 40 ml/h. The internal temperature did not rise above -74°C. The orange solution was stirred at -78°C for 30 minutes prior to the addition of anthranilonitrile (0.6 eq.) as a solution in THF. The reaction was warmed to 0°C and stirred for 2 hours. 3N HCl was added to the mixture and stirring continued for 30 minutes. The reaction was diluted with ethyl acetate and the layers were separated. The aqueous layer was back-extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via HPLC eluting with 93:7 hexanes/ethyl acetate.

C₁₃H₁₀FNO (MW = 215.24); mass spectroscopy found (M+H) 216.3.

¹H NMR (300 MHz, CDCl₃) δ 7.44-7.19 (6H, m), 6.74 (1H, d, J=8.0 Hz), 6.61 (1H, dd, J=0.94, 7.9 Hz), 6.10 (2H, bs).

Step B - Preparation of 2-[N-(α-Isopropylthio)-N'-(benzyloxycarbonyl)-glycinyl]-amino-3'-fluorobenzophenone

A solution of α-(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* 1975, 31, 863.) in dry THF was cooled to 0°C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C, the cooling bath was removed

and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C. A solution of 2-amino-3'-fluorobenzophenone (0.9 eq.) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous NaHCO₃, and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15→20% ethyl acetate/hexanes giving an off-white foam.

10 C₂₆H₂₅N₂O₄S (MW = 480.60); mass spectroscopy found (M+NH₄⁺) 498.3.
1H NMR (300 MHz, CDCl₃) δ 11.39 (1H, s), 8.59 (1H, d, J=6.0 Hz), 7.63-7.55 (2H, m), 7.48-7.27 (9H, m), 7.14 (1H, dt, J=1.2, 8.4 Hz), 5.94 (1H, d, J=7.2 Hz), 5.58 (1H, d, J=8.7 Hz), 5.17 (2H, ABq, J=14.7 Hz), 3.25 (1H, sep, J=6.6 Hz), 1.44 (3H, d, J=6.0 Hz), 1.28 (3H, d, J=6.6 Hz).

15

Step C - Preparation of 2-[N-(α-Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone

Ammonia gas was bubbled into a solution 2-[N-(α-isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) in THF at 20 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4 hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated *in vacuo*. The crude solid was used in step D without further 25 purification.

Step D - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

2-[N-(α-Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) was treated with glacial acetic acid and ammonium acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 30 hours. After concentrating the reaction in vacuo, the residue was partitioned

between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

$\text{C}_{23}\text{H}_{18}\text{FN}_3\text{O}_3$ (MW = 403.44); mass spectroscopy found (M+H) 404.4.

Anal. calcd for $\text{C}_{23}\text{H}_{18}\text{FN}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 66.98; H, 4.64; N, 10.18. Found: C, 67.20; H, 4.64; N, 9.77.

10 Step E - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

15 $\text{C}_{24}\text{H}_{20}\text{FN}_3\text{O}_3$ (MW = 417.47); mass spectroscopy found (M+H) 418.3.

Anal. calcd for $\text{C}_{24}\text{H}_{20}\text{FN}_3\text{O}_3$: C, 69.06; H, 4.83; N, 10.07. Found: C, 69.33; H, 4.95; N, 9.82.

20 Step F - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam which was used immediately in Step G.

25 Step G - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

30 Following General Procedure D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

$\text{C}_{24}\text{H}_{27}\text{FN}_4\text{O}_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.3.

Anal. calcd for $C_{24}H_{27}FN_4O_4$: C, 63.42; H, 5.99; N, 12.33. Found: C, 63.34; H, 6.01; N, 12.08.

Step H - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material was used immediately.

Example 8-K

Synthesis of
3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-
5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 2-Amino-4'-fluorobenzophenone

A solution of 4-bromofluorobenzene (1 eq.) in THF was cooled to -78°C under nitrogen and treated with *tert*-butyllithium (2.05 eq., 1.6 M solution in pentane) at a rate of 40 ml/h. The internal temperature did not rise above -74°C . The orange solution was stirred at -78°C for 30 minutes prior to the addition of anthranilonitrile (0.6 eq.) as a solution in THF. The reaction was warmed to 0°C and stirred for 2 hours. 3N HCl was added to the mixture and stirring continued for 30 minutes. The reaction was diluted with ethyl acetate and the layers were separated. The aqueous layer was back-extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC eluting with 93:7 hexanes/ethyl acetate.

$\text{C}_{13}\text{H}_{10}\text{FNO}$ (MW = 215.24); mass spectroscopy found (M+H) 216.3.

Anal. calcd for $\text{C}_{13}\text{H}_{10}\text{FNO}$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.80; H, 4.51; N, 6.74.

Step B - Preparation of 2-[N-(α -Isopropylthio)-N'-(benzyloxycarbonyl)-glycyl]-amino-4'-fluorobenzophenone

A solution of α -(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863.) in dry THF was cooled to 0°C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C, the cooling bath was removed and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C. A solution of 2-amino-4'-fluorobenzophenone (0.9 eq.) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous NaHCO₃, and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15→20% ethyl acetate/hexanes giving an off-white foam.

C₂₆H₂₅N₂O₄S (MW = 480.60); mass spectroscopy found (M+NH₄⁺) 498.2.

¹H NMR (300 MHz, CDCl₃) δ 11.28 (1H, s), 8.56 (1H, d, J=8.4 Hz), 7.78-7.73 (2H, m), 7.61-7.53 (2H, m), 7.36-7.32 (5H, m), 7.20-7.14 (3H, m), 5.98 (1H, d, J=7.5 Hz), 5.57 (1H, d, J=7.8 Hz), 5.16 (2H, ABq, J=14.7 Hz), 3.25 (1H, sep, J=6.0 Hz), 1.43 (3H, d, J=6.3 Hz), 1.27 (3H, d, J=6.6 Hz).

Step C - Preparation of 2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-4'-fluorobenzophenone

Ammonia gas was bubbled into a solution 2-[N-(α -isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) in THF at 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4 hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated *in vacuo*. The crude solid was used in step D without further purification.

Step D - Preparation of 3-(Benzyloxycarbonyl)amino-2,3-dihydro-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-4'-fluorobenzophenone (1 eq) was treated with glacial acetic acid and ammonium acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 hours. After concentrating the reaction in vacuo, the residue was partitioned
5 between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

10 C₂₃H₁₈FN₃O₃ (MW = 403.44); mass spectroscopy found (M+H) 404.4.
Anal. calcd for C₂₃H₁₈FN₃O₃•1.25H₂O: C, 64.85; H, 4.85. Found: C, 64.80; H, 4.55.

15 Step E - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

20 C₂₄H₂₀FN₃O₃ (MW = 417.47); mass spectroscopy found (M+H) 418.2.
Anal. calcd for C₂₄H₂₀FN₃O₃: C, 69.06; H, 4.83; N, 10.07. Found: C, 69.35; H, 4.93; N, 9.97.

25 Step F - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(4-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam which was used immediately in Step G.

30 Step G - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaniny]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

$C_{24}H_{27}FN_4O_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.4.

5 Anal. calcd for $C_{24}H_{27}FN_4O_4 \cdot 1.5H_2O$: C, 59.86; H, 6.28; N, 11.64. Found: C, 60.04; H, 5.62; N, 11.27.

Step H - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

10 Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material was used immediately.

15 Example 8-L

Synthesis of
3-(N'-L-Alaninyl)amino-2,3-dihydro-1-isobutyl-5-phenyl-1H-1,4-benzodiazepin-2-one

20 Step A: 1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (prepared according to the procedure of M. G. Bock et al., *J. Org. Chem.* **1987**, **52**, 3232-3239) was alkylated with isobutyl iodide using General Procedure 8-G to afford 1,3-dihydro-1-isobutyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

25 Step B: Following General Procedures 8-D and 8-F and using the product from Step A, 3-amino-1,3-dihydro-1-isobutyl-5-phenyl-2H-1,4-benzodiazepin-2-one was prepared.

30 Step C: The product from Step B and N-Boc-L-alanine (Sigma) were coupled using General Procedure D, followed by removal of the Boc group using General Procedure 8-J, to afford 3-(N'-L-alaninyl)amino-1,3-dihydro-1-isobutyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

By substituting isopropyl iodide, *n*-propyl iodide, cyclopropylmethyl iodide and ethyl iodide for isobutyl iodide in Step A above, the following additional intermediates were prepared:

5 3-(N'-L-alaninyl)amino-1,3-dihydro-1-isopropyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(N'-L-alaninyl)amino-1,3-dihydro-1-propyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(N'-L-alaninyl)amino-1,3-dihydro-1-cyclopropylmethyl-5-phenyl-2H-1,4-benzodiazepin-2-one

10 3-(N'-L-alaninyl)amino-1,3-dihydro-1-ethyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Example 8-M

Synthesis of

15 3-(N'-L-Alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

Step A: 1,3,4,5-Tetrahydro-5-phenyl-2H-1,5-benzodiazepin-2-one (CAS No. 32900-17-7) was methylated using General Procedure 8-I to afford 1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one.

20

Step B: Following General Procedures 8-E and 8-F and using the product from Step A, 3-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one was prepared.

25

Step C: The product from Step B and N-Boc-L-alanine (Sigma) were coupled using General Procedure D, followed by removal of the Boc group using General Procedure 8-N, to afford 3-(N'-L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one.

30

Example 8-N

Synthesis of

3-(N'-L-Alaninyl)amino-2,4-dioxo-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

3-Amino-2,4-dioxo-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 131604-75-6) was coupled with N-Boc-L-alanine (Sigma) using General Procedure D, followed by removal of the Boc group using General Procedure 8-N, to afford the title compound.

5

Example 8-O

Synthesis of

3-((R)-Hydrazinopropionyl)amino-2,3-dihydro-1-methyl-5-phenyl)-1H-1,4-benzodiazepin-2-one

10

3-Amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one was coupled to (R)-N,N'-di-BOC-2-hydrazinopropionic acid (Example N) using General Procedure D. Removal of the Boc group using General Procedure 5-B afforded the title compound.

15

Example 8-P

Synthesis of

3-Amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

20

Step A: - **Synthesis of 2,4-Dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

2,4-Dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 49799-48-6) was prepared from 1,2-phenylenediamine (Aldrich) and malonic acid (Aldrich) using the procedure of Claremon, D. A.; et al, PCT Application: WO 96-US8400 960603.

25

Step B: - **Synthesis of 2,4-Dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

2,4-Dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 113021-84-4) was prepared following General Procedure 8-M using the product from Step A and 2-iodopropane (Aldrich). Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to 1:1), then recrystallization from EtOAc/hexanes.

30

Step C: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-K using the product from Step B, 3-azido-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 186490-50-6) was prepared as a white solid. The product was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide a separable 23:1 mixture of pseudo-axial/pseudo-equatorial azides. The pure pseudo-axial azide was used in the next step.

Step D: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step C, 3-amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 186490-51-7) was prepared as a white solid. Purification was by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5). The isolated pseudo-axial amine atropisomer was completely converted to the pseudo-equatorial amine atropisomer by heating in toluene to 100-105 °C for 15 minutes, and the pseudo-equatorial amine atropisomer was used in the next step. The isomers were distinguished by ¹H-NMR in CDCl₃. Selected ¹H-NMR (CDCl₃): Pseudo-axial amine 4.40 (s, 1H); Pseudo-equatorial amine 3.96 (s, 1H).

Example 8-Q

Synthesis of 3-(R-2-Thienylglyciny)amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Step A: - Synthesis of N-(*t*-Butoxycarbonyl)-R-2-thienylglycine

N-(*t*-Butoxycarbonyl)-R-2-thienylglycine (CAS No. 74462-03-1) was prepared from L-α-(2-thienyl)glycine (Sigma) by the procedure described in Bodansky, M. et al; *The Practice of Peptide Synthesis*; Springer Verlag; 1994, p. 17.

Step B: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-R-2-thienylglyciny]-amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure J above using the product from Example 8-P and the product from Step A above, 3-[N'-(*t*-butoxycarbonyl)-R-2-thienylglyciny]-amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (9:1 gradient to 5:1).

Step C: - Synthesis of 3-(R-2-Thienylglyciny)amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step B, the title compound was prepared as a white solid.

Example 8-R

**Synthesis of
3-(L-Alaniny)-amino-2,4-dioxo-1,5-bis-methyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

2,4-Dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 23954-54-3) was prepared following General Procedure 8-M using the product from Example 8-P, Step A and iodomethane (Aldrich). The white solid product precipitated during partial concentration of the reaction after work-up, and was isolated by filtration.

Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

For this substrate, General Procedure 8-K was modified in the following manner. Initially the product from Step A was suspended (not a solution) in THF at -78°C, and following addition of the KN(TMS)₂ solution, this suspension was allowed to warm to -35°C over a period of 12 minutes, during which the suspension became a solution, and was re-cooled to -78°C; then

5 treated as described in the General Procedure. 3-Azido-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was purified by flash chromatography eluting with $\text{CHCl}_3/\text{EtOAc}$ (7:1), then trituration from hot CHCl_3 with hexanes and cooled to -23°C . The product was isolated as a white solid.

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

10 Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The crude product was used without further purification.

Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

15 Following General Procedure I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash
20 chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (2:1 gradient to 1:1).

Step E: - Synthesis of 3-(L-alaninyl)-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

25 Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an off-white amorphous solid.

Example 8-S

**Synthesis of
3-(L-Alaninyl)amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

30 2,4-Dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared following General Procedure 8-M using the

product from Example 8-P, Step A and 1-iodo-2-methylpropane (Aldrich). Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to 1:1), then recrystallization from EtOAc/hexanes.

5 Step B: - **Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure 8-K (a precipitate formed during the addition of the $\text{KN}(\text{TMS})_2$, but dissolved upon addition of the trisyl azide) using the product from Step A, 3-azido-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The product was purified by flash chromatography eluting with hexanes/EtOAc (4:1) and a second flash chromatography eluting with CH_2Cl_2 /hexanes/EtOAc (10:10:1 gradient to 8:6:1).

15 Step C: - **Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with CH_2Cl_2 /MeOH (98:2 gradient to 95:5, with 5% NH_3 in the MeOH).

Step D: - **Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

25 Following General Procedure I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH_2Cl_2 /EtOAc (3:1 gradient to 3:2).

30

Step E: - **Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an amorphous white solid.

Example 8-T

Synthesis of

3-(S-Phenylglyciny)amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Step A: - **Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-S-phenylglyciny]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure J above using the product from Example 8-S, Step C and the Boc-L-phenylglycine (Novabiochem, CAS No. 2900-27-8), 3-[N'-(*t*-butoxycarbonyl)-S-phenylglyciny]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (9:1 gradient to 5:1).

Step B: - **Synthesis of 3-(S-Phenylglyciny)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Following General Procedure 8-N above using the product from Step A, 3-(S-phenylglyciny)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine hydrochloride was prepared as an off-white solid.

Example 8-U

Synthesis of

3-(L-Alaniny)amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Step A: - **Synthesis of 2,4-Dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

2,4-Dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared following General Procedure 8-M using the product from Example 8-P, Step A, and (bromomethyl)cyclopropane (Lancaster).

Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to straight EtOAc), then recrystallization from EtOAc/hexanes.

5 Step B: - **Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

For this substrate General Procedure 8-K was modified in the following manner. Initially the product from Step A was suspended (not a solution) in THF at -78°C, and following addition of the KN(TMS)₂ solution, this suspension was allowed to warm to -30°C, during which the suspension became a solution, and was re-cooled to -78°C. Upon re-cooling to -78°C a precipitate began to form, therefore the reaction flask containing the mixture was partially raised above the cooling bath until the internal temperature rose to -50°C; then the trisyl azide solution was added. The cooling bath was removed and the mixture allowed to warm to -20°C whereupon the mixture had become a nearly homogenous solution, and the AcOH was added. Then, treated as described in the general procedure. 3-Azido-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was purified by trituration with hot to room temperature EtOAc, followed by recrystallization from hot to -23°C CHCl₃/EtOAc/EtOH (5:5:1) and isolated as a white solid.

20

Step C: - **Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5, with 5% NH₃ in the MeOH) followed by recrystallization from warm CH₂Cl₂/hexanes (1:1) to -23°C.

25

30 Step D: - **Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N³-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (3:1 gradient to 2:1).

Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an off-white solid.

Example 8-V

Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

To a stirred suspension of the product from Example 8-P, Step A (1.0 eq., 17.08 g) in DMSO (500 mL) at room temperature was added neopentyl iodide (43.01 g, 2.24 eq., Aldrich) and Cs₂CO₃ (72.65 g, 2.3 eq., Aldrich). The resulting mixture was heated to 75°C for 30 minutes, then additional Cs₂CO₃ (31.59 g, 1.0 eq.) was added and the mixture rapidly stirred at 75°C for 6 hours. The mixture was allowed to cool and H₂O (500 mL) and EtOAc (1000 mL) were added. The phases were partitioned and the organic phase washed with H₂O (1x500 mL), 1 M aq. HCl (2x500 mL), and brine (1x500 mL). Then, the organic phase was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography eluting with hexanes/EtOAc (3:2 gradient to 2:3) to provide 2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine as a white solid.

Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-K using the product from Step A, 3-azido-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The product was purified by flash chromatography eluting with hexanes/CH₂Cl₂/EtOAc (10:5:1 gradient to 5:5:1) to provide a separable 13:1 mixture of pseudo-axial/pseudo-equatorial azides. The pure pseudo-axial azide was used in the next step. Selected ¹H-NMR (CDCl₃): Pseudo-axial azide 5.12 (s, 1H); Pseudo-equatorial azide 4.03 (s, 1H).

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5, with 5% NH₃ in the MeOH). The isolated white solid product was identified as a ~4:1 mixture of pseudo-axial and pseudo-equatorial amines atropisomers by ¹H-NMR. The mixture was heated in toluene to 100 °C for 20 minutes, then re-concentrated to provide the pure pseudo-equatorial amine atropisomer, as a white solid, and this was for the next step. Selected ¹H-NMR (CDCl₃): Pseudo-axial amine 4.59 (s, 1H); Pseudo-equatorial amine 4.03 (s, 1H).

Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (4:1 gradient to 5:2).

Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an off-white solid.

Example 8-W

**Synthesis of
3-(L-Alaninyl)amino-2,4-dioxo-1,5-bis-phenyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine hydrochloride**

**Step A: - Synthesis of 2,4-Dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-
1H-1,5-benzodiazepine**

This procedure is a modification of the procedure described in Chan, D. M. T. *Tetrahedron Lett.* **1996**, 37, 9013-9016. A mixture of the product from Example 8-P, Step A (1.0 eq., 7.50 g), Ph_3Bi (2.2 eq., 41.26 g, Aldrich), $\text{Cu}(\text{OAc})_2$ (2.0 eq., 15.48 g, Aldrich), Et_3N (2.0 eq., 8.62 g) in CH_2Cl_2 (100 mL) was stirred under N_2 at room temperature for 6 days (monitoring by TLC). The solids were removed by filtration through a plug of Celite rinsing with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (3x75 mL). The filtrate was concentrated, dissolved in hot $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1) and filtered through a large plug of silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1, 2L). The filtrate was concentrated and the residue purified by flash chromatography eluting with straight CH_2Cl_2 gradient to $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1). 2,4-Dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine crystallized during concentration of the fractions containing the product, and was isolated by filtration as a white solid.

**Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-
tetrahydro-1H-1,5-benzodiazepine**

For this substrate, General Procedure 8-K was modified in the following manner. Initially the product from Step A was suspended (not a solution) in THF at -70°C , and following addition of the $\text{KN}(\text{TMS})_2$ solution, this suspension was allowed to warm to -20°C over a period of 10 minutes, during which the suspension became a solution, and was re-cooled to -70°C ; then treated as described in the general procedure. The title compound was purified by trituration with hot $\text{CHCl}_3/\text{hexanes}$ (1:1) to yield 3-azido-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine as a white solid.

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2 gradient to 95:5, with 5% NH_3 in the MeOH).

Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (4:1 gradient to 3:1).

Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as a white amorphous solid.

Example 8-X

Synthesis of 3-Amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following the method of R. G. Sherrill et al., *J. Org. Chem.*, 1995, 60, 730-734 and using glacial acetic acid and HBr gas, the title compound was prepared.

Example 8-Y

Synthesis of 3-(L-Valinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Synthesis of 3-[N'-(*tert*-Butylcarbamate)-L-valinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate (Example 8-B, Step A) was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-valine following General Procedure D to give the title compound.

$C_{26}H_{32}N_4O_4$ (MW 464.62); mass spectroscopy 464.3.

Anal. Calcd for $C_{26}H_{32}N_4O_4$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.29; H, 6.79; N, 11.20.

10 **Step B - Synthesis of 3-(L-valinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one**

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2-one, the title compound was prepared as a white foam.

15 $C_{21}H_{23}N_4O_2$ (MW 363.48); mass spectroscopy (M+H) 364.2.

Example 8-Z

20 **Synthesis of
3-(L-*tert*-Leucinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one**

Step A - Synthesis of 3-[N'-(*tert*-Butylcarbamate)-L-*tert*-leucinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

25 (S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate (Example 8-B, Step A) was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-*tert*-leucine following General Procedure D to give the title compound.

$C_{27}H_{35}N_4O_4$ (MW 479.66); mass spectroscopy 479.

30

Step B - Synthesis of 3-(L-*tert*-Leucinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-L-*tert*-leucinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2-one, the title compound was prepared as a white foam.

Anal. Calcd for $C_{22}H_{25}N_4O_2 \cdot 0.5H_2O$: C, 68.19; H, 7.02; N, 14.40. Found: C, 68.24; H, 7.00; N, 14.00.

Example 8-AA

Synthesis of 3-(L-Alaninyl)-amino-2,3-dihydro-1,5-dimethyl- 1H-1,4-benzodiazepine

2,3-Dihydro-1,5-dimethyl-1H-1,4-benzodiazepine was prepared following General Procedures 8-I (using methyl iodide), 8-D and 8-F. Coupling of this intermediate with Boc-L-alanine (Novo) using General Procedure D, followed by deprotection using General Procedure 5-B afforded the title compound which was used without further purification.

Example 8-AB

Synthesis of 3-(L-3-Thienylglycinyl)amino-2,4-dioxo- 1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro- 1H-1,5-benzodiazepine

Step A: - Synthesis of N-(*t*-Butoxycarbonyl)-L-3-thienylglycine

N-(*t*-Butoxycarbonyl)-L-3-thienylglycine was prepared from L- α -(3-thienyl)glycine (Sigma) by the procedure described in Bodansky, M. et al; *The Practice of Peptide Synthesis*; Springer Verlag; 1994, p. 17.

Step B: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-3-thienylglycinyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure D above using the product from Example 8-V, Step C and the product from Step A above, 3-[N'-(*t*-butoxycarbonyl)-L-3-thienylglycinyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared.

Step C: - Synthesis of 3-(L-3-Thienylglyciny)amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-N above using the product from Step B, the title compound was prepared.

Example 8-1

Synthesis of
3-(3,5-Difluorophenylacetyl)amino-
2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure A above using 3,5-difluorophenylacetic acid (Oakwood) and 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one (Example 8-X), the title compound was prepared as a solid having a melting point of 236-239°C. The reaction was monitored by tlc on silica gel ($R_f = 0.7$ in 10% methanol/dichloromethane) and purification was by silica gel chromatography using 10% methanol/dichloromethane as the eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.4$ (m, 9H), 6.90 (dd, $J = 6.0, 2.2$, 2H), 6.73 (dt, $J = 6.6, 2.2, 2.2, 6.6$, 1H), 5.50 (d, $J = 7.7$, 1H), 3.68 (s, 2H), 3.46 (s, 3H).

^{13}C -nmr (CDCl_3): $\delta = 172.9, 165.2, 163.5, 138.3, 133.6, 127.7, 126.4, 125.4, 124.6, 123.9, 120.3, 117.2, 108.2, 107.9, 98.4, 62.8, 38.6, 30.9$.

$\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_2\text{F}$ (MW = 419); mass spectroscopy (MH^+) 420.

Example 8-2

Synthesis of
3-(N'-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-
2,3-dihydro-1-ethyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure A above using N-(3,5-difluorophenylacetyl)-L-alanine (Example B) and 3-amino-2,3-dihydro-1-ethyl-5-phenyl-1H-1,4-benzodiazepin-2-one (prepared as described in Example 8-X using ethyl iodide), the title compound was prepared as a solid having a melting point of 155-158°C. The reaction was monitored by tlc on silica gel ($R_f = 0.48$ in 10% methanol/dichloromethane) and purification was by silica gel chromatography

using 10% methanol/dichloromethane as the eluant, followed by recrystallization from diethyl ether.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.73 (d, J = 7.7, 1H), 7.4 (m, 9H), 6.86 (m, 2H),
5 6.68 (m, 1H), 6.58 (d, J = 7.2, 1H), 5.43 (dd, J = 2.7, 4.9, 2.7, 1H), 4.67
(m, 1H), 4.3 (m, 1H), 3.7 (m, 1H), 3.52 (s, 2H), 1.46 (dd, J = 6.6, 6.6, 3H),
1.10 (dt, J = 7.1, 1.1, 6.0, 3H).

¹³C-nmr (CDCl₃): δ = 167.8, 164.8, 163.4, 161.3, 136.7, 133.6, 127.6,
126.4, 125.2, 124.0, 118.1, 107.8, 98.3, 95.5, 62.9, 44.7, 38.6, 14.5, 8.7.

10 C₂₈H₂₆N₄O₃F₂ (MW = 504); mass spectroscopy (MH⁺) 505.

Example 8-3

Synthesis of

15 3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-
2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure D above using N-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and 3-amino-1,3-dihydro-5-phenyl-2H-1,4-
benzodiazepin-2-one (CAS: 103343-47-1. Sherrill, R. G.; Sugg, E. E. *J. Org.*
Chem. **1995**, *60*, 730.), the title compound was prepared as a white solid.

20 Purification was by trituration with 1:1 ether/hexanes.

C₂₆H₂₁F₂N₄O₃ (MW = 475.51); mass spectroscopy (MH⁺) 476.

Anal. Calcd for C₂₆H₂₁F₂N₄O₃: C, 65.54; H, 4.65; N, 11.76. Found: C,
65.37; H, 4.67; N, 11.63.

25

Example 8-4

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-
2,3-dihydro-1-methyl-5-(1-piperidinyl)-1H-1,4-benzodiazepin-2-one

30 Following General Procedure D above using N-(3,5-difluorophenylacetyl)-
L-alanine (Example B) and 3-amino-1,3-dihydro-1-methyl-5-(1-piperidinyl)-2H-
1,4-benzodiazepin-2-one (Example 8-A), the title compound was prepared as a
white solid having a melting point of 154-160°C.

C₂₆H₂₉F₂N₅O₃ (MW = 497.60); mass spectroscopy 497.

Anal. Calcd for $C_{26}H_{29}F_2N_5O_3$: C, 62.75; H, 5.89; N, 14.08. Found: C, 62.52; H, 5.81; N, 13.62.

Example 8-5

5

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one (Example 8-C), the title compound was prepared as a white solid having a melting point of 126.5-130°C.

$C_{27}H_{23}ClF_2N_4O_3$ (MW = 524.1); mass spectroscopy 523.7.

Anal. calcd for $C_{27}H_{23}ClF_2N_4O_3$: C, 61.78; H, 4.42; N, 10.67. Found: C, 61.92; H, 4.52; N, 10.46.

Example 8-6

20

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (Example 8-D), the title compound was prepared as a white solid.

25

$C_{27}H_{22}BrF_3N_4O_3$ (MW = 587.43); mass spectroscopy 587.

Anal calcd for $C_{27}H_{22}BrF_3N_4O_3$: C, 55.21; H, 3.78; N, 9.54. Found: C, 55.25; H, 4.00; N, 9.72.

Example 8-7

30

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-N'-methyl-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(N'-methyl-L-alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one (Example 8-E), the title compound was prepared as a white solid.

5 ^1H NMR (300 MHz, CDCl_3): δ = 7.65 (1H, d, J =7.9 Hz), 7.59-7.34 (8H, m), 7.23 (1H, t, J =7.2 Hz), 6.84 (2H, d, J =6.0 Hz), 6.65 (1H, t, J =7.2 Hz), 5.46 (1H, d, J =7.9 Hz), 5.42 (1H, d, J =7.2 Hz), 3.78 (2H, s), 3.47 (3H, s), 3.02 (3H, s), 1.42 (3H, d, J =7.1 Hz).

$\text{C}_{28}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_3$ (MW = 505.2051); mass spectroscopy 505.2046.

10

Example 8-8

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one

15 Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one (Example 8-F), the title compound was prepared as a white solid.

$\text{C}_{27}\text{H}_{22}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_3$ (MW = 559.43); mass spectroscopy 559.2.

20 Anal. calcd for $\text{C}_{27}\text{H}_{22}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_3$: C, 57.97; H, 3.96; N, 10.02. Found: C, 57.99; H, 3.98; N, 9.92.

Example 8-9

Synthesis of

3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

25 Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one (Example 8-G), the title compound was prepared as a white solid.

30

$\text{C}_{27}\text{H}_{30}\text{F}_2\text{N}_4\text{O}_3$ (MW = 497.2364); mass spectroscopy 497.2370.

Example 8-10

Synthesis of
3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-
2,3-dihydro-1-methyl-7-nitro-5-phenyl-
1H-1,4-benzodiazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one (Example 8-H), the title compound was prepared as a yellow solid.

¹H NMR (300 MHz, CDCl₃): δ = 8.44 (1H, dd, J=2.2, 9.0 Hz), 8.42 (1H, dd, J=2.3, 9.0 Hz), 8.23 (2H, d, J=2.6 Hz), 7.73 (2H, m), 7.56-7.40 (12H, m), 6.83 (4H, m), 6.69 (2H, m), 6.37 (2H, apt, J=7.8 Hz), 5.45 (1H, d, J=7.7 Hz), 5.44 (1H, d, J=7.7 Hz), 4.71 (2H, m), 3.56 (2H, s), 3.55 (2H, s), 3.52 (3H, s), 3.51 (3H, s), 1.47 (3H, d, J=7.0 Hz), 1.46 (3H, d, J=7.0 Hz).

C₂₇H₂₃F₂N₅O₅ (M+H = 536.1747); mass spectroscopy found 536.1749.

Example 8-11

Synthesis of
3-[N'-(3,5-Difluorophenylacetyl)-L-alaninyl]-amino-
2,3-dihydro-1-methyl-5-(2-fluorophenyl)-
1H-1,4-benzodiazepin-2-one

Following General Procedure D above using 3,5-difluorophenylacetic acid (Oakwood Products, Inc.) and 3-(L-alaninyl)-amino-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (Example 8-I), the title compound was prepared as a white solid having a melting point of 185-188°C.

C₂₇H₂₃F₃N₄O₃ (MW = 508.54); mass spectroscopy found (M+H) 509.3.

Anal. calcd for C₂₇H₂₃F₃N₄O₃: C, 63.78; H, 4.53; N, 11.02. Found: C, 63.99; H, 4.49; N, 10.84.

Example 8-12

Synthesis of
3-[N'-(3,5-Difluorophenyl-α-hydroxyacetyl)-L-valinyl]-amino-
2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one